BIRTH WEIGHT PERCENTILE BY GESTATIONAL AGE AND MATERNAL FACTORS THAT AFFECT BIRTHWEIGHT IN SINGAPORE

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TABLE OF CONTENTS

List of Tables

List of figures

ABSTRACT

A. Introduction

Gestational age-specific birthweight growth curve is an essential tool for neonatal studies. Birthweight provides valuable information to both obstetricians and paediatricians on the intrauterine growth of neonates. It also provides a snapshot of the regional population distribution for the monitoring of epidemiological outcomes and public health care policies.

B. Objectives

The aim of this study is to develop a gestational age-specific birthweight growth curves and percentile charts for infants in Singapore relevant to its three major ethnic groups - Chinese, Malay and Indian. We intend to identify factors which might influence birth weight such as maternal age, parity, antenatal disease, Assisted Reproductive Techniques (ART) pregnancies as well as infant gender and ethnicity.

C. Materials and Methods

Data was collected and analyzed from maternity records of 21,656 infants born at the National University Hospital (NUH), Singapore, from 2000 - 2008. Descriptive statistics were used to examine the birthweight distributions and determine the mean and percentile distribution for each gestational age with respect to ethnicity. The effect of gestational age was illustrated by smoothed birthweight growth curve in weeks of gestation using quantile regression. Male and female birthweight growth curves were graphically overlaid to better illustrate observed differences, and selected points on the curves were compared and quantified in the

corresponding tables. In order to study the effect of ethnicity, birthweight growth curves were also graphically overlaid for further analysis. The mean birthweight were also calculated by gestational age and ethnic groups. Analysis of variance (ANOVA) was performed to search for statistical significance between groups. Linear Regression was used to evaluate the trends over time for the period of 8 years. Mixed Model analysis was used to analyze the independent effects of gender, ethnic group, maternal age, parity, gestational age, ART pregnancy and various maternal diseases (gestational diabetes, anemia and hypertension) on birth weight.

D. Results

Two versions of gestational age-specific birthweight growth curves and percentile charts were developed. The first version presents growth curves and percentiles chart for birthweights with gestational ages from 26 – 41 weeks, consolidated for both genders. A second version for a more specific gestational window of 34 – 41 weeks presents birthweight growth curves and percentiles chart, now segregated by both gender and ethnicity.

Chinese babies were found to be at least 53.2g heavier than the Indians ($P < 0.001$) and 38.3g heavier than the Malays ($P < 0.001$). However, no significant differences were observed in the birthweight between the Malays and Indians. Significant prediction for smaller babies was found in mothers under the age of 20, primigravidas and women who conceived via ART or developed gestational hypertension.

E. Discussion

The establishment of updated gestational age-specific birthweight growth curves and percentile charts suited for the local clinical profile allows both obstetricians and paediatricians to better assess neonatal health. Maternal factors like age, parity and maternal diseases as well as ethnicity all affect birth weight. These findings are a useful reference for future research that will help to improve perinatal health.

CHAPTER 1 INTRODUCTION

A formal association between birth weight and disease was first observed by DJ Barker in adults with ischaemic heart disease, and termed the ‘thrifty hypothesis’ (*Barker et al., 1989*). Further evidence derived from various studies demonstrated that malnourishment during intrauterine life is associated with a lower birth weight, as well as the increased risk of cardiovascular disease (*Barker et al.,1989*), type 2 diabetes (*Lithell et al.,1996)* (*Hales et al., 1991*) (*Martyn et al., 1998*) and adiposity (*Gluckman et al., 2008; Kensara et al., 2005*) in later life. Moreover, birth weight is an important determinant of infant survival in their early life (*Godfrey and Barker., 2000*). As such, the definition of birth weights appropriate for the local ethnic populations in Singapore is crucial for the subsequent determination of factors that influence birth weight, and by extension, risk for future metabolic and cardiovascular conditions.

An individual’s birth weight provides valuable information to both obstetricians and paediatricians on the intrauterine growth of a neonate. At a population level, the statistical reviews of local birthweights are also informative for the monitoring of epidemiological outcomes and public health care policies. Studies have demonstrated significant ethnicity-related variations in birth weight (*Cheng et al., 1972*) (*Hughes et al., 1986*) (*Viegas et al., 1989*) yet many hospitals primarily employ the World Health Organisation (WHO) guidelines for low birth weight (LBW) infants (under 2500 grams at birth) to identify high risk intrauterine growth restricted (IUGR) infants (*World Health Organisation, 2004*). By these measures, ethnic variations are not accounted for, limiting the utility of birth weight measures for the appropriate clinical assessment of infants.

In order to reflect ethnic and other variations more carefully for improved local accuracy, it is crucial to have a diverse sample of infants when creating birthweigth growth curves. The frequency of at least three major ethnic groups (Chinese, Malay and Indian) in Singapore's populace offers a unique opportunity to investigate the effect of ethnicity on birth weight, with a concomitant reduction in other confounding factors such as access to medical care and basic maternal nutrition.

In this study, we also sought to investigate the birth weight trend over the past decades and also identify factors which significantly influence birth weight, with a long term aim of determining if improvements to early-life events might be preventive against chronic disease in later adulthood.

CHAPTER 2 LITERATURE REVIEW

2.1 The Importance of Birthweight

As a commonly recorded statistic at hospital births, birth weight is one of the most available population variables to explain infant mortality and later morbidity (*Wilcox et al., 2001*). Additionally, birth weight is strongly associated with appropriate childhood development (*Liu et al., 2001*) as well as risks for various diseases in adulthood such as cardiovascular disease (*Miura et al., 2001*). Many researches on birth weight have focused on the assumption that birth weight is a major determinant of infant survival (*Draper et al., 1999*) (*Wilcox et al., 1983*). Such strong observed links are suggestive that a biological mechanism that impacts birth weight also has influence on subsequent survival and human health.

At birth, both weight and gestational age are the two most common parameters used to assess the maturity of the newborn. Controversy over the perceived utility of one parameter over the other as a single indicator of fetal development continues to be debated. While it is believed that gestational age is an important criteria for assessing risk factors, monitoring health status in populations and evaluating interventions aimed at decreasing perinatal mortality and preterm delivery (*Alexander et al., 1997*). The determination of gestational age, commonly defined by the woman's last menstrual period, is subject to much recall bias (*Pearl et al., 2007*). Instead, early ultrasonography has been regarded as the gold standard for estimating gestational age (*Dietz et al., 2007*). Thus consistent refinement in the measurement of quality data is essential in providing more accurate analysis.

Comparatively, birth weight would be a more reliable and convenient parameter to measure newborn maturity. However, definitions of intrauterine growth restriction (IUGR) and small for gestational age (SGA), clinical diagnoses for infants with low birthweights relative to a WHO profile, are based on simple statistical approaches that may misclassify infants with a normal developmental profile and vice versa**.** As such, stratification of birthweights by gestational age allows for better assessment of infants who are physiologically small but not necessarily premature. It is proven that gestational age is a major contributor to birth weight, and there is a strong link between birth weight and perinatal mortality at each fixed gestational age (*Wilcox et al, 1992*). Moreover, gestational age correlates in a positive and linear manner with birth weight for normal developing healthy baby. Hence it makes more biological sense to incorporate both parameters in assessing the effect of fetal growth and retardation on clinical outcomes and survival.

2.2 Types of Birthweight Growth Curves

There are two main types of birthweight growth curves, defined either as a standard or a reference curve. While standard curves simply illustrate the optimal growth, a reference curve describes the actual growth of the sample population. Both types of curves can be created using either cross-sectional or longitudinal data (*Wright., 2002*). Cross-sectional curves describe a sample at one point in time whereas longitudinal curves follow a sample over time, demonstrating growth status with time. In this thesis, we refer to these as sub-categories of birthweight growth curves.

For preterm infants, cross-sectional curves represent intrauterine growth while longitudinal curves represent post-natal growth. Intrauterine growth curves, also defined as preterm growth curves, best describe the *in utero* growth of fetuses derived from the cross-sectional data of birth sizes of preterm and term infants. Hence intrauterine growth curves reflect the best estimations of optimal fetal growth, a useful tool for growth assessment (*Olsen et al., 2010*).

The first growth curves for birthweight as a function of gestational age were created by Lubchenco et al. in 1963 (*Lubchenco et al., 1963*). These growth curves were intended to discriminate preterm from full-term low birthweight (LBW) infants who face greater mortality risks (*Battaglia et al., 1967*). The first birthweight growth curve for Singapore was published in 1972 by Cheng et al (*Cheng et al., 1972*) using data from the Kandang Kerbau Hospital. Since then, no updates have been made to these birthweight growth curves till 2009, with a revised birthweight growth curve that takes maternal stature into account. (*Tan et al., 2009*)

Despite vast differences between Caucasian and Asian infants (*Madan et al., 2002*), birthweight growth curves and distributions determined in a Caucasian population are still the primary reference for fetal growth measurements in Singapore. Birthweight by gestational age can be influenced by many factors such as ethnicity, socioeconomic status, gestational diabetes, hypertension, smoking, maternal height and weight, maternal age, and infant's gender. Birthweight may predict growth over the first years of life (*Binkin et al., 1988*) and may be a risk factor for future medical conditions such as hypertension (*Zhao et al., 2002*).

Standard growth curves may lead to incorrect estimates of the number of 'large for gestational age' (LGA) and 'small for gestational age' (SGA) infants. Because males are generally born with a higher mean birthweight than females (*Storms and Howe., 2004*), birthweight growth curves that are not gender-specific can result in an overestimation of male LGA infants, or underestimation of female LGA infants. Customized birthweight centiles for specific population subsets may be needed to identify newborns truly at risk (*Rowan et al., 2009*). In order to determine the proper criteria for LGA and SGA in the local Singapore population, we need to analyse the data for birthweight, gestational age, and gender of the newborns.

2.3 The Use of Birthweight Growth Curves

2.3.1 Identification of Low Birthweight (LBW) Infants

Birthweight growth curves are used to classify infants based on their birthweight and gestational age. These classifications are essential in assessing growth status in both public health and clinical settings. To reduce the public health burden, the percentage of LBW infants in the population is ideally reduced, and birthweight growth curves are often used in epidemiological studies to chart this progression. Low birthweight is commonly caused by intrauterine growth restriction (IUGR), preterm birth (before 37th week of gestation) or the combination of these 2 factors, and is a common indicator of perinatal risk. The World Health Organization (WHO) defines an IUGR infant as one with birthweight of less than 2500g, a classification widely used by health professionals all over the world (*World Health Organization, 1992*). Because LBW babies have a 20 times higher risk of infant mortality than their average weight counterparts, the LBW condition maybe an association or result of the process responsible for increased morbidity and mortality (*MacDorman et al., 1999*). Through improved medical interventions, infant mortality rates have drastically declined in developed countries. As such, LBW infants are also associated with perinatal and later metabolic dysregulation risk.

With the emergence of the "thrifty hypothesis" by DJ Barker, LBW is not only a proxy for perinatal health outcomes but also associated with poor cognitive development and adult health, thought to be caused by intrauterine programming of the fetus. Evidence from various studies demonstrate the increased risk of cardiovascular disease, type 2 diabetes and adiposity in ageing individuals previously subjected to *in utero* malnourishment and subsequent LBW (*Barker et al., 1989*)

(*Lithell et al., 1996*) (*Hales et al., 199*1) (*Martyn et al., 1998*) (*Gluckman et al., 2008*) (*Kensara et al., 2005*). While many factors contribute to the occurrence of LBW in infants, the contribution to LBW incidence from preterm delivery or fetal growth retardation is preventable through early diagnosis and intervention, in agreement with population healthcare goals to reduce infant mortality and ill-health.

2.3.2 Identification of Intrauterine Growth Restricted (IUGR) and Small-for-Gestational-Age (SGA) Infants.

The main purpose of developing birthweight birthweight growth curves and charts is to better identify infants who fail to reach their growth potential while in the mother's womb, a condition commonly known as intrauterine growth restriction (IUGR), through a retrospective comparison of birthweight with eventual IUGR outcomes (*Gardosi et al., 2009*). As such, a clear clinical definition of the IUGR condition is necessary for accurate correlations between this condition and its predictive risk from birthweight. A subtle but often ignored distinction exists between small-for-gestational-age (SGA) and IUGR diagnoses. Not all SGA fetuses are pathologically growth restricted and may in fact be constitutionally small, due to other considerations such as maternal size constraint (*Groom et al., 2007*). SGA is a statistical definition, used for neonates whose birthweight falls below the 10th percentile for its particular gestational age *(Battaglia et al., 1967*). Although most IUGR infants are also SGA, a small minority of IUGR infants have birthweights above the 10th percentile. Despite their apparently average birthweights for gestational age, these morphological IUGR infants face an altered growth trajectory and risks, and should be more correctly managed as IUGR infants.

The assessments of the infant’s size by reference to a population standard are useful for routine clinical comparisons and epidemiological research, but are insufficient for diagnosis and treatment of the IUGR condition. Instead, ultrasound scanning provides the most reliable and important information about the fetal growth and well-being, and can be used to determine a likely IUGR condition (*Peleg et al., 1998*). With the use of umbilical artery Doppler Velocimetry in high-risk pregnancies with maternal hypertension, or other situations resulting in possible impairment of fetal growth, the use of umbilical cord Doppler Velocimetry has been a useful tool to assess fetal progress, and is associated with reduced perinatal deaths as well as improved diagnosis of a perinatal outcome in preterm SGA infants (*Young et al., 2009*).

More recently, researchers have turned to the placenta for further assessments. As an organ key for proper fetal development, the placenta provides a rich source of information to understand underlying causes related to fetal growth (*Salafia et al., 2006*). Large population studies are required for accurate statistics on overall perinatal mortality, given its relatively low population incidence. Birthweight and gestational age are common parameters for defining normal limits (eg. 10^{th} and 90^{th} centile) for different ethnic populations (*Roberts et al., 1999)* (*McCowan et al., 2004*) (*Rios et al., 2008*) (*Festini et al., 2004*) (*Arbuckle et al., 1993*) (*Hsieh et al., 2006*). However, the cut-off scores used to define SGA and IUGR are arbitrary, and do not take into account individual variation that could otherwise differentiate between physiological and pathological smallness. Instead, the use of customised standards improves the degree to which adverse outcome is linked to preceding growth potential. Thus these observations from the birthweight growth curves and charts shed light on the various significant effects of IUGR.

2.4 The Impact of Birthweight - Intrauterine Programming

The impact of birthweight can extend well beyond infancy. According to fetal origins hypothesis (*Barker et al., 1998)*, fetal malnutrition for which LBW is a marker, may induce a long-term or permanent change to the physiology, morphology or metabolism of a fetus, in response to a specific stimulus at critical periods in development. These changes may affect developmental outcomes through processes such as reduced cell numbers or alterations to cell type composition (*Ozanne et al., 2002*) (*Moritz et al., 2003*) (*Holemans et al., 2003*) (*McMillen et al., 2005*). Many studies show that intrauterine environment programmes adult disease susceptibility by altering the epigenetic state of the fetus genome, affecting phenotype without need for changes to the DNA sequence (*Vickaryous et al., 2005*). Environmental influences such as maternal nutrition and stress during development can affect the methylation of DNA (*Lillycrop et al., 2009*). Accumulated DNA methylation errors can lead to premature epigenetic ageing, contributing to an increased susceptibility of diabetes and other chronic metabolic diseases in later life (*Rodríguez-Rodero et al., 2010*). Some of these epigenetic modifications may also be inherited transgenerationally (*Gluckman et al., 2009*). This is observed in the predisposition towards a thrifty phenotype associated with decreased placental weight and restricted fetal growth is actually genetically determined. Besides posing an immediate threat for fetal and neonatal survival, the IUGR condition is one with much farther reaching consequences on adolescent and adult life.

2.5 Birthweight: Influence of Gender and Ethnicity

Differences in birthweight can be influenced by gender and ethnicity, and in this study, we were interested in significant differences between local ethnic groups. Because large ethnic differences in birthweight were already evident in the initial data, we anticipated an immediate need to create ethnicity-specific birthweight growth curves, so as to accurately define percentile cutoffs for SGA, Appropriate-for-gestational-age (AGA) and LGA, and improve the relevance of future public health interventions.

2.5.1 Gender Differences in Birthweight

Males are generally at greater risk of being born premature than their female contemporaries, face an associated increase in infant mortality rates (Males 22%, Females 15%), or adverse neonatal outcomes, including neurodevelopmental impairment (*Astofli and Zonta., 1999*) (*Stevenson et al., 2000*) (*Hintz et al., 2006*).

Male infants tend to be larger than females by 128g at birth (values adjusted for gestational age at birth) (Kramer et al., 1990) (*Storms and Van Howe., 2004*). Even at earlier gestational stages, this gender contribution to size is already evident. Between 20 to 30 weeks of gestation, male infants were larger than females as measured by weight, length and head circumferences (*Hindmarsh et al., 2002*). These findings suggest that gender-specific birthweight growth curves are also important for accurate diagnosis.

2.5.2 Ethnic Differences in Birthweight

Ethnic differences in health reveal important etiological mechanisms in the pathway to disease. It is also valuable to identify specific groups that require special care and benefit from the healthcare system. Therefore, understanding the ethnic disparities in birth outcome and infant health is of priority. Despite drastic improvements in neonatal health, significant differences in mean birthweight still persist. Birthweight is a key indicator to an infant's health at birth, as well as mother's reproductive health. As a strong predictor for infant mortality risk, it is also informative of ethnic group differences in infant survival.

Dissecting the historical mean birthweight for individual ethnic groups in decade-long intervals, disparities in birthweight are evident. In the 1980s, Viegas et al. reported that the mean birthweight for the Chinese infants in Singapore was 3228g, about 90g and 132g less than the mean birthweight of Malay and Indians infants respectively. The percentage of births below 2500g was almost twice as high in the Indians as it was in the Chinese (*Viegas et al., 1989*). In the 1990s, Malay infants overtook Indian infants, with the highest mean birthweight of 3140g among the three major ethnic groups in Singapore. The larger birthweight of Malays could be accounted for by the higher mean parity and mean BMI compared to the other two ethnic groups (*Tan et al., 2009*).

In all studies, the mean birth weight of Indian is significantly smaller than Chinese and Malay (*Cheng et al., 1972*) (*Hughes et al., 1986*) (*Viegas et al., 1989*) (*Tan et al., 2009*) Paradoxically, while Indians have the highest proportion of LBW infants among the three ethnic groups, the infant mortality risk of these individuals is lower than expected for their birthweight (*Gould et al., 2003*) (*Lee et al., 2010*). The lower birthweight of Indians compared to other ethnic groups is well documented in studies conducted in Singapore (*Cheng et al., 1972*) (*Hughes et al., 1984*) (*Hughes et al., 1986*) (*Viegas et al., 1989*).

Given the largely limited contribution of differing healthcare or nutritional access among ethnic groups in Singapore, it is not immediately apparent why LBW infants are more prevalent in the Singapore Indian group, apart from ethnicity (*Hughes et al., 1986*). Instead, these observations point towards differing ethnic norms in average birthweight, possibly arising from subtle genetic differences between ethnic groups that result in phenotypic variation. As such, the lower body size norms of specific ethnic groups are not reflective of adverse influences on growth and development, and appropriate adjustments to cutoffs for the LBW condition is necessary (*Hughes et al., 1984*).

Observations on ethnic differences in birthweight were conducted on small sample size across three decades that saw large economic changes in the local society (*Millis et al., 1954*) (*Cheng et al., 1972*) (*Hughes et al., 1986*) (*Viegas et al., 1989*) (*Tan et al., 2009*). Therefore, socio-economic differences are likely to confound any conclusions made from ethnic data consolidated across these time points. Instead, birthweight comparisons of different ethnic groups residing in similar social situation would be more reliable (*Hughes et al., 1986*). Improved healthcare status and antenatal care reduces the incidence of LBW infants, independent of ethnicity, as suggested by a local study of Indian infants where the percentage of LBW infants declined from 11.5% to 6.1% in the years 1967-1974 and 1981-1983 respectively (*Hughes et al., 1984*). Thus it would be interesting to see if ethnic differences still remain in the current developed nation of Singapore.

2.6 Maternal Factors That Affect Birthweight

The increasing prevalence of metabolic diseases reflects an escalating cost and burden to society. Metabolic diseases such as hypertension, diabetes, insulin resistance, renal and cardiovascular disease are a few such diseases traditionally attributed to lifestyle factors such as obesity. However these diseases may also be programmed *in utero*, resulting from exposure to a sub-optimal *in utero* environment. Various other maternal factors may contribute significantly to the programming of an offspring's disease phenotype. These observations highlight the importance maintaining the maternal condition before and during gestation. Maternal health and well-being, including nutritional or dietary intake, and the incidence of obesity or gestational diabetes, are just a few of the important parameters which may need to be monitored more carefully during pregnancy.

2.6.1 Maternal Factors

A. Age

Birth statistics over recent decades show a definite worldwide trend of delaying parenthood until the thirties and beyond. This is partially attributable to the increasing numbers of career-minded women and living costs in developed economies such as Japan and Europe (*Suzuki et al., 2006)* (*Han-Peter and Billari Jos´e., 2002*). However, an increasing phenomenon of concern is the emergence of "elderly primigravidae". The Council of International Federation of Obstetrics defines it as "*one aged 35 or more at first delivery"* which is deemed appropriate for the current inclination of pregnancy (*Schmitz et al., 1958).* Advancing maternal age is associated with various obstetric complications including antepartum hemorrhage, pre-clampsia, diabetes mellitus and preterm birth (*Chan et al., 2008*). Maternal age alone is an independent risk factor for a perinatal mortality, intrauterine fetal death, and neonatal death. Elderly primigravidae have higher rates of antepartum, intrapartum and newborn complications compared to young nulliparas aged between 25-29 years old (*Prysak et al., 1995)*. Increasingly, healthcare policies must take these demographic changes and resultant healthcare needs into consideration when formulating diagnostic and treatment plans.

B. Ethnicity

The contribution of ethnicity to birthweight extends beyond genetic differences in ethnicities alone, but can also be attributed to differences in maternal nutrition, environment, age, parity, maternal height, weight and social-economic status. Ethnicity accounts for differences average birthweight and risk of low birthweight both in Singapore and elsewhere, though these differences are largely unexplained (*Hughes et al., 1986*) (*Viegas et al., 1989*) (*Shiono et al., 1997*) (*Sherman et al., 1993*). Ethnic inequalities in health have been linked to socioeconomic disadvantage (*Kelly et al., 2008*). However, some studies have failed to establish socioeconomic and behavioural explanations for ethnic differences in birthweight (*Sherman et al., 1993*). However, this apparent lack of evidence has led some to suggest that lower birthweights in certain ethnic groups are a result of normal variation in fetal growth constraints, as evident in Indian populations which show an increased incidence of LBW infants (*Gould et al., 2003*) (*Shiono et al., 1986*). An improved means of identifying clinically significant LBW infants in each ethnic group will contribute to overall advancements in infant health across the population.

C. Parity

Parity has significant impact on birth weight. It is widely known that primiparous women are at increased risk of neonatal morbidity, perinatal death and any obstetric complication (*Bai et al., 2002*). With increasing parity, birthweight also increases markedly (*Millis et al., 1954*). In agreement, the proportion of LBW infants declined from the first birth to the third births and increased with increasing birth order (Hughes et al). Older primiparas were at elevated risk for SGA but no association between age and SGA was found in multiparas (Lisonkova *et al., 2010*). Maternal age and parity should be studied as effect modifiers in order to obtain valid estimates of risk as well as the understanding of the varying effects of parity and age (Lisonkova *et al., 2010*). The elevated risk of SGA for older primiparous mothers requires a more vigilant monitoring of their health status during pregnancies to prevent intrauterine growth restriction as increase in the prevalence of chronic conditions (including cardiac disease, diabetes and hypertension) can be observed among this group of pregnant patients (Lisonkova *et al., 2010*).

D. Social-Economic Status

Results have shown that the association of socio-economic variables and birthweight could influence the variation of growth in children (*Emaneul et al., 2004*) (*Mohammadzadeh et al., 2010*). Socioeconomic status is one of the most powerful risk factors for poor health outcomes. The rate of LBW/SGA is consistently increased among the socioeconomic deprived groups, a result of multiple factors (*McCowan et al., 2009*). The influence of maternal malnutrition on birthweight has gained special interest in view of the possibility of developing IUGR (*Neel et al., 1991*). On a related note, the mother's nutritional situation is also directly associated with her socio-economic status (*Martorell et al., 1987*) (*Andersson et al., 1997*).

However, social-economic status is not a consistent predictor for perinatal outcomes. Some authors have argued that much of the relationship between socioeconomic status and perinatal outcome is dependent on a spectrum of factors such as family income, educational levels and lifestyle factors (*Joseph et al., 2007*). Though socioeconomic conditions can impact for individual behavior, the ranges of outcomes are too varied for accurate consideration (*Parker et al., 1994*). Though there is an existing intervening role in the relationship between socioeconomic status and birth outcome, we cannot deny its importance as a contributor to birthweight.

E. Marital Status

Marital status could be a significant risk factor for low birth weight and preterm births. In one example, unmarried women are likely to face higher stress about their pregnancy. Coupled with reduced or absent support from partners, these factors may have a negative effect on perinatal outcome (*Masho et al., 2010*). Highlighting the difficulties in resolving the contribution of varied personal situations in a personal context, conflicting data exists regarding the correlated risk between LBW/SGA and marital status. The increased risk of infant mortality associated with single motherhood is neither consistent among social and demographic subgroups (*Bennett et al., 1994*), suggesting that marital status is better combined with other risk factors to study their association with birth outcome. Ethnicity was considered a stronger marker of risk for infant mortality than marital status as reported by Bennett et al. However, unmarried, cohabiting and single women have small but significant increases in SGA after adjustment for confounding factors (including parity, smoking, alcohol consumption, infertility, abortions, previous fetal death, time since previous pregnancy and maternal illness) (*Raatikainen et al., 2005*). Nonetheless, health care professionals should be aware of the implications of paternal presence and marital status which may indirectly affect the incidence of preterm births and low birth weight among such women.

F. Stature

Maternal height, weight and BMI are well recognized as important factors determining birth weight, with a positive correlation between these morphometric parameters and increased birthweight (*Tan et al., 2009*). Besides influencing birth weight, low maternal BMI is associated with poor infant survival while higher BMI is associated with gestational diabetes (*Cogswell and Yip., 1995*) (*Leung et al., 2008*). Several other studies have reported that shorter women have increased risk for SGA babies (*Zhang X et al., 2010*), while mothers of SGA infants were shorter and had lower prepregnancy body weights than mothers of AGA infants, size for gestational age uncorrected for maternal stature and not necessarily indicative of a clinical presentation (*Thompson et al., 2001*).

Interestingly, McCowan et al found that mothers of SGA babies were shorter, lighter, had lower body mass indices and were more likely to be nulliparous than women whose babies were SGA by both customised and population criteria (*McCowan et al., 2005*). Therefore it is advisable to use customised centiles to detect more babies at risk of perinatal morbidity and mortality than would be detected by population centiles.

G. Maternal Birthweight

Though a woman's own birthweight is correlated with the eventual birthweight of their own children, the degree to which this impacts fetal growth is still unclear. SGA, preterm birth and IUGR appear to be a familial trait, as exemplified by the doubled risk of SGA mothers themselves giving birth to SGA infants, independent of maternal adult stature and other known risk factors for SGA (*Klebanoff et al., 1997*). Separately, a combined association was found between maternal and infant birthweights, as well as infant survival, suggesting that this risk of perinatal mortality is compounded through generations (*Skjaerven et al., 1997*). Hence, the knowledge of a woman's own birthweight would be useful to predict the outcome of her own pregnancies.

2.6.2 Maternal Substance Exposure

A. Smoking

A definite, well-established relationship exists between smoking and low birth weight. It is well known that women who smoke in pregnancy have smaller babies than non-smokers. Many studies have shown that cigarette smoking has a dose-dependent and causative relationship with LBW, SGA and preterm births (*Chan A et al., 2001*) (*Bernstein et al., 2005*). However, the most adverse effects of smoking may be reversible if smoking is stopped early in pregnancy. Women who stopped smoking before 15 weeks of gestation did not show increased rates of spontaneous preterm birth and SGA infants as compared to their non-smoker counterparts (*McCowan et al., 2009*). These encouraging results suggest that continued efforts aimed at reducing cigarette consumption in pregnant smokers are warranted throughout pregnancy and can lead to improvements in birth weight, even when these reductions occur later in pregnancy.

B. Alcohol

Heavy alcohol consumption is associated with a spectrum of disorders, including LBW, preterm birth, congenital abnormalities, fetal alcohol syndrome and adverse post-natal behaviour (*Jaddoe et al*, *2007*). Still the effect of moderate alcohol use on birthweight is limited, with statistical evidence for lowered infant birthweights only in mothers who consumed alcohol within the first trimester, or combined this alcohol consumption with >20 cigarettes smoked per day. In this subgroup, the average birth weight ratio of women consuming more than 120 g alcohol per week was 7.2% lower than that of abstainers (*Verkerk et al., 1993*).

Taking into account gestational age, infant sex, maternal age, parity, weight, and height, and cigarette smoking, a separate study also suggested that a daily alcohol consumption of three drinks of more was associated with a significant reduction in birthweight (*Larroque et al., 1993*). However, the limited available evidence suggests that drinking within the guideline levels set for pregnant women is unlikely to have any significant effect on the child. Good antenatal care, good diet, refrain from alcohol drinking, and not smoking are also very important in containing risk and providing a healthy environment for the unborn child.

2.6.3 Maternal Medical Conditions

A. Hypertension

Hypertension during pregnancy leads to increased risk of adverse pregnancy outcome and poor perinatal outcome. Ananth et al. has reported that hypertensive disorders in pregnancy were associated with SGA infants, with risk differences of 5.1%, 3.5%, and 9.2% for chronic hypertension, pregnancy-induced hypertension, and eclampsia, respectively (*Ananth et al., 1995*). Pre-eclampsia is co-occuring in approximately 40% of pregnancies of women with hypertension and has the most severe outcome *(Heard et al., 2004)*. Vreeburg et al. also reported that those with pre-existing hypertension has the lowest risk of adverse perinatal and maternal outcome (with odd ratios (OR) 1.26-2.90); pregnancy hypertension held the intermediate position (OR 1.52-5.70), while superimposed pre-eclampsia was associated with the highest risk (OR 2.00-8.75) (*Vreeburg et al., 2004*).

Much effort has been made to better predict pre-eclampsia before its full onset, but no present effective prophylatic methods exist. As a result, gestational hypertension and preeclampsia continue to be major obstetric problems, accounting for a large number of maternal and perinatal morbidities cases (*Sibai, 2003*). If the likehood of a woman developing severe pre-eclampsia is high, increased surveillance during pregnancy and early appropriate management will help to safeguard the health of both mother and infant.

B. Diabetes

Babies born to mothers with gestational diabetes are at an increased risk of problems such as macrosomia which may lead to delivery complications (*Casey et al., 1997*). Maternal diabetes during pregnancy also increases the risk of childhood and adult obesity, diabetes and cardiovascular disease in their offspring (*Moore, 2010*). Since fetal macrosomia is related to postprandial but not fasting glucose, postprandial glucose measurements should routine in diabetes care during pregnancy. A target 1-h postprandial glucose value of 7.3 mM (130 mg/dl) may be the level that optimally reduces the incidence of macrosomia without increasing the incidence of small-for-gestational-age infants (*Combs et al., 1992)*. This treatment of gestational diabetes is important in attenuating the risk to the fetus of acquiring metabolic syndrome in later adult life.

2.7 Assisted Reproductive Technology (ART) Pregnancy

With increased maternal age and falling fertility rates, the number of women undergoing assisted reproductive techniques (ART) treatment has increased in recent years. It is widely known that ART carries more risks and accounts for the rise in multiple births as well as LBW and premature births among singletons (*Schieve et al., 2002*). The incidence of congenital abonormalities and perinatal complications is also increased in ART infants, and include epigenetic disorders such as Beckwith-Wiedemann and Angelman syndrome (*Shiota et al., 2005*) (*Williams et al., 2009*). On a population level, this has longer term implications on the health outcomes of upcoming generations.

While technological improvements in ART can aid in reducing the overall risk to infant development, some adverse perinatal outcomes in ART pregnancies may in fact be explained by maternal factors (*Shiota et al., 2005*). Women who conceive via ART are more likely elderly primigravidae, and may carry multi-pregnancy, due to the current re-implantation guidelines to maximize conception likelihood per treatment. Since the reduction in multiple pregnancies does improve the perinatal outcome, much of the emphasis on new ART techniques has been geared to artificially produce single births rather than multiples (*Romundstad et al., 2008)*. However, further understanding of biological effects on infertility and ovarian stimulation is required in the hope to reduce adverse effects on infant health.

CHAPTER 3 MATERIALS AND METHODS

A total of 21,656 births were registered in the National University Hospital (NUH) of Singapore from 1 January 2000 to 31 December 2008, and de-identified data was obtained from the Department of Obstetrics and Gynaecology. From this data, two versions of updated birthweight growth curves were created. The first version illustrates combined gender birthweight growth curves for percentiles for gestational ages from 26 - 41 weeks. A second version of curves further stratifies the data by gender and ethnic groups for a subgroup of infants from gestational ages 34 - 41 weeks. Birthweight growth curves were smoothed to better reflect the average growth of the population, and minimize the contribution of data outliers to the overall conclusions. The birthweight growth curves generated in this study reflect desirable infant growth progressions, and are intended to be used in as a prognostic clinical tool.

The data set was analysed for the influence of gender and ethnicity on birthweight. In order to analyse the ethnic differences in birth weight, we included only 19,634 live singletons with mother from the well-defined ethnic group, ie Chinese, Malay or Indian ethnic group. Those without defined maternal ethnic classification were omitted from the study cohort. Many studies have proved that differences in birthweight have been shown between gender and ethnicity. Therefore further analysis into these differences was performed in this study. The differences that were found were explored and explanations were attempted by controlling for the available variables in the database.

Another important aim of the study was to identify maternal factors that significantly affect birthweight. The maternal factors from the study cohort were categorized to include ethnicity, maternal age, parity, maternal diseases (diabetes, anemia and hypertension) and ART pregnancy. Maternal ethnicity was categorized into three defined ethnic groups (Chinese, Malay and Indian) as described in the above paragraph. Maternal age was categorized into five approximately proportionate groups of 21-25 years, 26-30 years, 31-35 years, 36-40 years and >=41 years. Parity was categorized as Parity 1, Parity 2, Parity 3 and Parity 4 or more. The following clinical parameters were used for diagnosis of maternal conditions in pregnancy: Gestational Hypertension (blood pressure >140/90 mm Hg), Anemia (Hemoglobin <11 g/dl), Gestational Diabetes (2h post-prandial glucose >7.8 mmol/L following an oral glucose tolerance test). The number of deliveries following ART with singleton birth was included for analysis. As discussed in the literature review previously, many factors can directly affect the well-being of the infant even at developmental stage while in mother's womb. Therefore variables with regards to maternal factors that were collected in this data set were analysed in order to find out more insights to improve perinatal health.

Birthweight growth curves were created in STATA v11.0 for Windows, with additional graphics created in RGui version 2.8.1 (available at http://www.r-project.org)

A full list of information surrounding the data is available in Table 30, Appendix C.

3.1 Measurement Methods

Birthweight measurements were performed by delivery suite nurses, within the first hour of birth, on a regularly calibrated digital scale. All the staff at delivery ward was trained in conducting birthweight measurements. Standardized measurement using digital scale has been used for the past 9 years.

Gestational age was determined by routine ultrasound in early pregnancy. In the absence of early ultrasound, gestational age was estimated using the last reported menstrual period.

3.2 Data Set Description

The NUH Maternity Database was established in 2000 to track prenatal care and births at NUH. Routine data collected included maternal race, age at delivery, education background, mode of delivery, parity and obstetric history as well as infant gender, birthweight and gestational age at birth (to the last completed week).

3.3 Preliminary Analysis

Step 1: Data Cleaning

Prior to analysis, 15 records with missing fields or entry errors for gender, gestational age and parity were removed from the data set.

Step 2: Establishment of Inclusion and Exclusion Criteria

A combined gender birthweight growth curve for gestational ages 26 - 41 weeks was created from available data; the gestational age window represented reflects the earliest to full term live births recorded at NUH. A second version of growth curves segregated by gender and ethnicity was generated from singleton full-term births (gestational ages from 34 - 41 weeks). 1021 infants from the initial data set used for the first curve were excluded, on account of mixed or undetermined ethnicity.

In order to rectify the point on relatively small population size for certain gestational age category to prevent skewed birthweight data; data from 26 - 41 weeks were deliberately chosen to generate respective percentile distribution of birthweight by gestational age. Main reason was because any other gestational age that is not within the range, the sample size was too small to give meaningful analysis. The exclusion criteria were to remove 376 set of multiple pregnancies as multiple infants can influence the birthweight of the infant. In addition to the exclusion, 63 deaths and 117 with congenital abnormalities were also excluded.

Step 3: Removal of Outliers

To identify and exclude erroneous data arising from recording errors, box and whisker plots of birthweight for each gestational age were generated for preliminary analysis (Figures 1 and 2). Outliers were identified by initial visual inspection and subsequent verification with the Tukey's method (*Tukey, 1977*) (*Arbuckle et al., 1993*). In this method, the 25th percentiles (*p*25) and 75th percentiles (*p*75) were computed for each gestational age group and a variable (*L* value), representing multiples of the interquartile range above *p*75 or below *p*25, was calculated. Birthweights with *L* value>1.5 were regarded as extreme outliers. This cutoff value of *L*1.5 defines outliers as entries with weights beyond 1.5 times the interquartile range below and above *p*25 and *p*75 respectively, and results in the exclusion of 1.6% of all infants in the set. Excluded individuals have improbable birthweight extremes for their gestational age, and all such data was recorded at earlier gestational ages (*Joseph et al., 2001*).

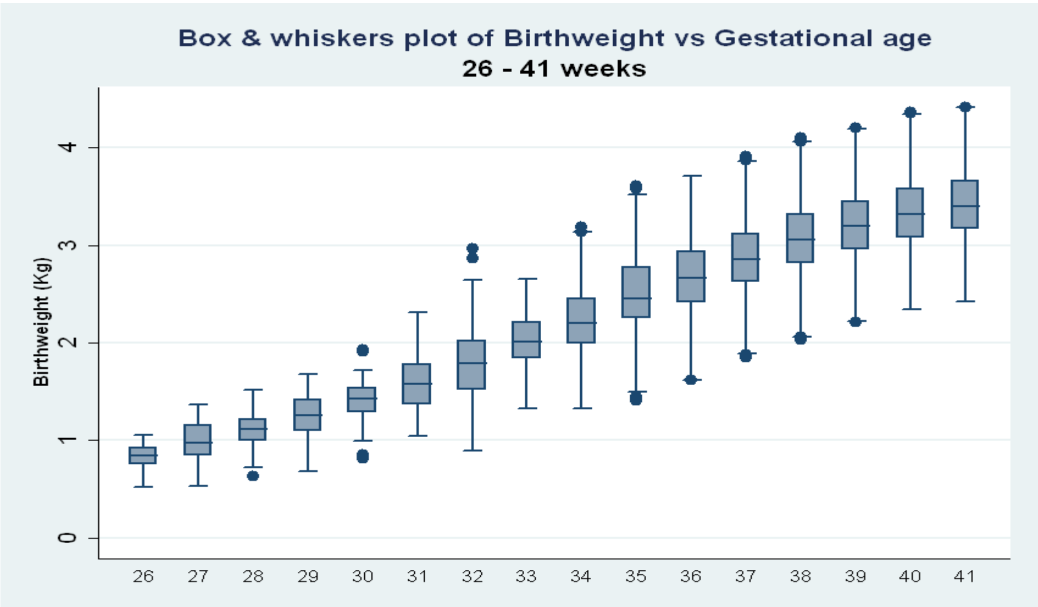
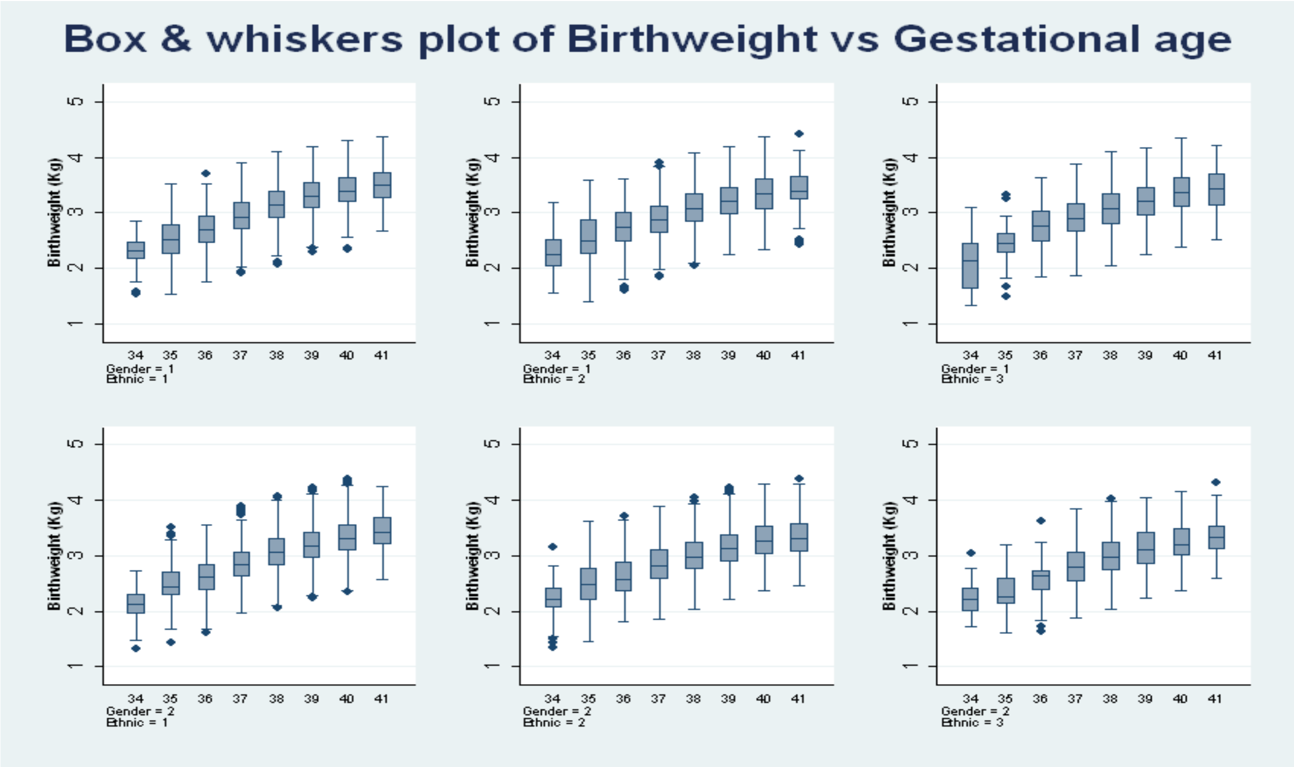


Figure 1: Box & whiskers plot of birthweight for gestational age of 26 - 41 weeks



Gender 1: Male; Gender 2: Female; Ethnic 1: Chinese; Ethnic 2: Malay; Ethnic 3: Indian

Figure 2: Box & whiskers plot of birthweight for gestational age of 34 - 41 weeks for male and female infants among the 3 ethnic groups.

3.4 Data Analysis for Birthweight Growth Curves

3.4.1 Birthweight Growth Curve Creation and Percentile Calculation

After applying the inclusion and exclusion criteria, descriptive statistics were used to examine the birthweight distributions, and determine the mean and percentile distribution (10^{th}, 50^{th}, 90^{th} percentiles) for each gestational age with respect to ethnicity. Tabulation of birthweight percentiles by gestational age, and segregated by gender and ethnicity are created.

With continuous variables such as birthweight and gestational age, growth curves are more advantageous for charting infant growth progressions, than are tabulated values alone. Following exclusion of outliers, smoothed growth curves were generated by Quantile Regression (QR) for five percentiles (10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th}) *(Koenker and Bassett., 1978*).

To smooth each birthweight percentile over gestational ages of 26 - 41 weeks, various polynomial models (second to third degree, with or without cubic spline) were tested. The final QR birthweight model utilized 3^{rd} polynomial degrees of gestational age (GA) with a single knotted cubic spline at the midpoint of the GA range.

In total, eight sets of birthweight growth curves were constructed. A combined gender birthweight growth curves of the 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentiles by gestational window of 26 - 41 weeks was created. Birthweight growth curves of 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentiles by gestational window of 34 - 41 weeks segregated by gender and ethnicity were also created. One chart for 10^{th}, 50^{th} and 90^{th} percentile distribution of birthweight by gestational age between 26 - 41 weeks for combined gender in the three ethnic groups was developed. Two more charts for 10^{th}, 50^{th} and

90th percentile distribution of birthweight by gestational age between 34 - 41 weeks for male and female infants among the three ethnic groups were also developed.

3.4.2 Comparison to Cheng's Birthweight Growth Curves

The first birthweight statistics for the local population were published in 1972, using data from the main maternity hospital in Singapore (*Cheng et al., 1972*). Subsequently, updated statistics were obtained from 1995 data originating from the same hospital (*Tan et al., 2009*). In this updated study, additional factors such as maternal height, weight and body mass index (BMI), were considered to have a significant impact on birthweight, and reflected in their updated birthweight percentile curves by gestational age.

While the birthweight curves of Tan et al are derived from more recent data, the inclusion of maternal factors into the curve precluded this from comparison with our updated birthweight growth curves. Instead, earlier data from Cheng et al was used for comparison. We first overlaid our updated birthweight growth curves with that from Cheng et al to visually identify differences. Thereafter, selected points were compared and are presented in Table 15 - 17. These comparisons were made only for our combined gender birthweight growth curve, since no precedent curves exist for gender or ethnic specific groups in Singapore.

3.4.3 Gender Analysis

To determine if significant differences in birthweight exist between the genders, male and female birthweight growth curves were overlaid for comparison, with specific comparisons performed at the 10^{th}, 50^{th} and 90^{th} percentiles by gestational age in Table 19. Gender-segregated mean differences in birthweight by gestational age were tested for statistical significance using *t*-tests.

3.4.4 Ethnicity Analysis

Birthweight and gestational age between the three major ethnic groups (Chinese, Malay, Indian) in Singapore were separately investigated for males and females. The ethnic group classifications were categorized as explained previously (Chapter 3 – Materials and Methods Section). Due to smaller sample sizes in some ethnic groups, gestational ages of less than 34 weeks and more than 41 weeks were omitted from this analysis.

The combined gender birthweight comparison among the ethnic groups and specifically analyzed at the 10^{th}, 50^{th} and 90^{th} percentile points were made (Figure 15). Gender comparisons were also made within each ethnic group, (Figure 16 - 18). For each gender, ethnicity-specific birthweight curves were overlaid to illustrate any evident differences (Figure 19 & 20). Differences between ethnic groups and gender-specific mean birthweights were considered for statistical significance using analysis of variance (ANOVA). Multiple linear regression analysis adjusted for maternal age, parity and diabetes were also done to explore the differences between ethnic groups and gender-specific mean birthweights.

3.5 Trend Analysis

Linear Regression was used to evaluate the rate of primiparity, low birthweight (LBW), maternal diseases (diabetes) and mean birthweight to model trends over the period of 8 years (from year 2000 – 2008).

3.6 Data Analysis for Maternal Factors

To simplify the interpretation of results, it is useful to divide values of a continuous variable (maternal age and parity) into categories. Mean birthweight for maternal factors were tabulated. Analysis of variance (ANOVA) was performed to search for statistical significance between groups for maternal age and parity. *t*-tests were performed to test statistical significances for categories .

Mixed Model analysis, taking into account babies from the same mother, was used to analyze the independent effects of gender, ethnic group, maternal age, parity, gestational age, ART pregnancy and various maternal diseases (gestational diabetes, anemia and hypertension) on birth weight. Mixed Model analysis, specifies within-group correlation structure in the data to the repeated measurements on the same subject over time. The repeated measures correlated were the individual mothers and the working correlation matrix was unstructured.

CHAPTER 4 RESULTS

4.1 Data Preparation

Prior to generating birthweight growth curves, the raw data was subjected to two rounds of exclusion criteria. The initial round first excluded 556 infants with conditions that may have resulted in an altered *in utero* growth trajectory (multiple births, stillborn, or have congenital abnormalities). An additional 20 records were incomplete and disregarded for future analysis. 1021 infants with unknown, mixed ethnicity or ethnicities beyond the three groups considered in this study were also excluded. Table 1 shows the results after this first round of exclusion.

In the second exclusion round, we chose to analyze only infants born between 26 - 41 gestational weeks, excluding 77 from further analysis. Additionally, significant outliers (1.7%) were identified with a cutoff of *L*1.5, and verified with Tukey's method (*Tukey, 1977*). These outliers fell outside of values 1.5 times the interquartile range below the first quartile (25^{th} percentile) and above the third quartile (75^{th} percentile) in birthweight for gestational age. Table 2 shows the result after second round of exclusion.

The final data set of 19,634 was used to create one updated reference birthweight growth curve and percentile chart. A subgroup of these initial records was used to stratify this data by both ethnicity and gender, for the gestational ages of 34 - 41 weeks. This final data set was also used for maternal factors analysis.

	No of infants removed	No of infants remaining
Original number of deliveries		21,656
Exclusion 1		
Death	63	1597
Congenital abnormalities	117	
Multiple pregnancies	376	
Unknown gender	4	
Unknown gestational age	9	
Unknown parity	5	
Duplicated sample ID	2	
Ethnic Others	1021	
After exclusion 1		20,059

Table 1: Results after exclusion 1

	No of infants removed	No of infants remaining
After exclusion 1		20,059
GA < 26 and > 41 weeks	77	
Tukey 1.5 cutoff		
Gestational age (GA)		
26	3	
27	2	
28	2	
29	7	
30	8	
31	8	
32	5	
33	10	348
34	12	
35	11	
36	17	
37	58	
38	70	
39	76	
40	33	
41	26	
After exclusion 2 (Final)		19,634

Table 2: Results after exclusion 2

4.2 Description of the Study Cohort

A. The NUH Maternity Database 2000 - 2008

The proportion of infants given birth in NUH did not increase drastically from year 2000 - 2008. The percentage of birth ranges from 10% to 12% over the 8 years.

Year	Frequency	Percentage (%)	Cumulative Percentage (%)
2000	2,187	11.1	11.1
2001	2,151	11.0	22.1
2002	2,445	12.4	34.5
2003	2,132	10.9	45.4
2004	2,046	10.4	55.8
2005	2,037	10.4	66.2
2006	2,136	10.9	77.1
2007	2,276	11.6	88.7
2008	2,224	11.3	100
Total	19,634	100	

Table 3: The number of birth in NUH, Year 2000 – 2008.

B. Ethnic Distribution

The Ethnic distribution for the study cohort of 19,634 infants comprising 8,718 (44.4%) Chinese, 7,336 (37.4%) Malay, 3,580 (18.2%) Indian.

Ethnic groups	Frequency	Percentage (%)	Cumulative Percentage (%)
Chinese	8,718	44.4	44.4
Malay	7,336	37.4	81.8
Indian	3,580	18.2	100
Total	19,634	100	

Table 4: The ethnic distribution in NUH, Year 2000 – 2008.

C. Maternal Age Distribution

Over the 8 years period, the highest rate of infants born to mothers with the age group of 26 - 30 years old (31.8%) followed by the age group of 31 – 35 years old (31.7%).

Age category	Frequency	Percentage (%)	Cumulative Percentage (%)
20 years old or less	898	4.6	4.6
21 – 25 years old	2,836	14.4	19.0
26 – 30 years	6,249	31.8	50.8
31 – 35 years	6,223	31.7	82.5
36 – 40 years	2,964	15.1	97.6
41 years or more	464	2.4	100
Total	19,634	100	

Table 5: Maternal Age Distribution of 19,634 mothers, Year 2000 – 2008.

Majority of the Chinese mother gave birth at older age group of 31 – 35 years old compared to the Malay and Indians who gave birth at a younger age of 26 – 30 years old.

Age Category	Frequency			Total
	Chinese	Malay	Indian	
20 years old or less	135	681	82	898
21 – 25 years old	656	1,673	507	2,836
26 – 30 years old	2,654	2,164	1,431	6,249
31 – 35 years old	3,396	1,685	1,142	6,223
36 – 40 years old	1,663	925	376	2,964
41 years old or more	214	208	42	464
Total	8,718	7,336	3,580	19,634

Table 6: Maternal age by ethnicity of 16,634 mothers, Year 2000 – 2008.

D. Parity

38.9% of the mothers are primiparous.

Parity	Frequency	Percentage (%)	Cumulative Percentage (%)
0	7,635	38.9	38.9
1	6,906	35.2	74.1
2	3,244	16.5	90.6
3	1,279	6.5	97.1
4 or more	570	2.9	100
Total	19,634	100	

Table 7: Number of mothers by parity, Year 2000 – 2008.

When comparing primiparous versus multiparous status, it was found that more Malay women were multiparous when compared to Chinese and Indian women.

Parity	Frequency			Total (%)
	Chinese (%)	Malay (%)	Indian (%)	
0	3,913 (44.9)	2,285 (31.2)	1,437 (40.1)	7,635 (38.9)
1	3,274 (37.6)	2,035 (27.7)	1,597 (44.6)	6,906 (35.2)
2	1,241 (14.2)	1,588 (21.6)	415 (11.6)	3,244 (16.5)
3	256 (2.9)	923 (12.6)	100 (2.8)	1,279 (6.5)
4 or more	34 (0.4)	505 (6.9)	31 (0.9)	570 (2.9)
Total	8,718 (100)	7,336 (100)	3,580 (100)	19,634 (100)

Table 8: Parity status of the 19,634 mothers according to ethnicity.

E. Maternal Diseases

There were 735 hypertensive cases, 1,459 diabetes cases and 231 anemia cases diagnosed among the mothers over the period of 8 years.

Age Category	**Frequency**			**Total**
	Chinese (%)	**Malay (%)**	**Indian (%)**	
Hypertensive diseases	318 (3.7)	330 (4.5)	87 (2.4)	735
Diabetes	704 (8.1)	405 (5.5)	350 (9.8)	1459
Anemia	40 (0.5)	155 (2.1)	36 (1.0)	231

Table 9: Number of women who have maternal disease during their pregnancies according to ethnicity.

F. Infant Characteristics

Overall, there were 674 more males (51.7%) than females (48.3%) among the infants born during the period of 8 years.

Gender	**Frequency**	**Percentage (%)**	**Cumulative Percentage (%)**
Male	10,154	51.7	51.7
Female	9,480	48.3	100
Total	19,634	100	

Table 10: Characteristics distribution for 19,634 infants born between 2000 – 2008.

The overall mean birthweight for this study population was 3078 g and most infants were born at 38.3 gestational weeks. Mean birthweight of male infants were statistically significant heavier than female infants by 74.2 g.

	Overall	Male	Female
Mean Birthweight (g)	3078.0	3113.8	3039.6
Gestational age (weeks)	38.3	38.2	38.4

Table 11: Mean birth weight and gestational age for the 19,634 infants.

4.3 Birthweight Growth Curves and Percentile Charts

Table 12 shows the 10^{th}, 50^{th} and 90^{th} percentile distribution of birthweight by gestational age between 26 to 41 weeks for the study cohort of 19,634 infants. Table 13 and 14 show the 10^{th}, 50^{th} and 90^{th} percentile distribution of birthweight by gestational age between 34 to 41 weeks for male and female infants in the three ethnic groups. From these tables, it is evident that all preterm babies (less than 37 completed weeks) were less than 2500g in the 10^{th} percentile range for male and female infants in three ethnic groups.

Figure 3 illustrates the birthweight growth curves of 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentiles by gestational ages between 26 - 41 weeks. Figure 4 illustrates the birthweight growth curves of 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentiles by gestational ages between 34 - 41 weeks. Figures 5 - 10 illustrate the birthweight growth curves of 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentiles by gestational ages between 34 - 41 weeks for male and female babies among the three ethnic groups. Further analysis on gender and ethnic differences was done and is discussed later in this section.

Gestational Age (weeks)	Number	Birthweight (g)		10th Percentile			50th Percentile			90th Percentile		
		Mean	± SD	Chinese	Malay	Indian	Chinese	Malay	Indian	Chinese	Malay	Indian
26	27	833.0	137.7	620	550	753	858	724	834	1043	897	946
27	40	979.8	221.6	608	745	722	929	1186	987	1226	1290	1206
28	41	1093.6	205.9	800	899	630	1085	1199	1020	1256	1454	1255
29	46	1224.2	268.6	815	1097	685	1252	1259	1049	1604	1595	1420
30	46	1407.7	234.1	1036	1133	1426	1338	1497	1551	1560	1914	1669
31	53	1587.0	291.8	1211	1151	1317	1672	1577	1447	1924	2100	1829
32	84	1808.7	427.7	1215	1471	1080	1845	1789	1771	2225	2615	2605
33	79	2023.7	291.2	1686	1627	1597	2015	2002	2155	2305	2400	2480
34	211	2214.5	367.1	1779	1810	1500	2218	2220	2165	2575	2700	2700
35	369	2506.9	423.8	1938	2025	2044	2455	2478	2425	3035	3150	2930
36	847	2666.7	392.2	2175	2155	2200	2655	2673	2690	3120	3225	3140
37	2538	2878.2	382.1	2420	2380	2360	2880	2840	2853	3390	3370	3415
38	5352	3073.6	371.6	2655	2575	2570	3105	3025	3020	3590	3555	3555
39	5434	3209.0	358.5	2805	2730	2690	3240	3165	3163	3690	3670	3665
40	3626	3335.8	369.4	2915	2835	2835	3354	3295	3280	3838	3825	3820
41	841	3412.8	363.8	3015	2920	2890	3440	3343	3350	3940	3825	3880
Total	19634											

Table 12: Birthweight percentile values (g) for 19,634 infants from gestational age of 26 - 41 weeks.

Gestational Age (weeks)	Number	Birthweight (g)		10th Percentile			50th Percentile			90th Percentile		
		Mean	± SD	Chinese	Malay	Indian	Chinese	Malay	Indian	Chinese	Malay	Indian
34	116	2243.9	382.7	1779	1810	1379	2323	2250	2138	2575	2790	2660
35	202	2536.2	410.2	2078	2125	1950	2510	2495	2455	2973	3220	3260
36	444	2719.7	390.7	2220	2195	2315	2700	2733	2755	3115	3295	3185
37	1358	2916.5	379.8	2470	2465	2445	2933	2883	2895	3455	3380	3485
38	2796	3117.9	374.2	2700	2630	2590	3135	3085	3073	3620	3610	3620
39	2795	3257.5	350.4	2880	2770	2765	3305	3205	3210	3740	3720	3670
40	1789	3383.4	369.7	2965	2860	2870	3395	3338	3358	3880	3855	3925
41	414	3451.4	363.8	3055	2955	2890	3500	3398	3425	4040	3820	3920
Total	9914											

Table 13: Birthweight percentile values (g) for male infants from gestational age of 34 - 41 weeks.

Gestational Age (weeks)	Number	Birthweight (g)		10th Percentile			50th Percentile			90th Percentile		
		Mean	± SD	Chinese	Malay	Indian	Chinese	Malay	Indian	Chinese	Malay	Indian
34	95	2178.5	345.6	1652	1787	1836	2122	2205	2215	2630	2700	2770
35	167	2471.4	438.2	1780	1955	2055	2440	2475	2265	3170	3140	2815
36	403	2608.2	386.0	2090	2120	2065	2605	2572	2630	3143	3168	2970
37	1180	2834.0	380.2	2385	2340	2313	2840	2805	2790	3275	3363	3350
38	2556	3025.1	362.6	2600	2550	2550	3060	2970	2980	3533	3500	3488
39	2639	3157.8	359.9	2745	2680	2645	3175	3125	3100	3625	3600	3665
40	1837	3289.4	363.3	2875	2805	2810	3300	3250	3195	3790	3750	3720
41	427	3375.3	360.4	2990	2880	2900	3410	3298	3325	3865	3855	3798
Total	9304											

Table 14: Birthweight percentile values (g) for female infants from gestational age of 34 - 41 weeks.

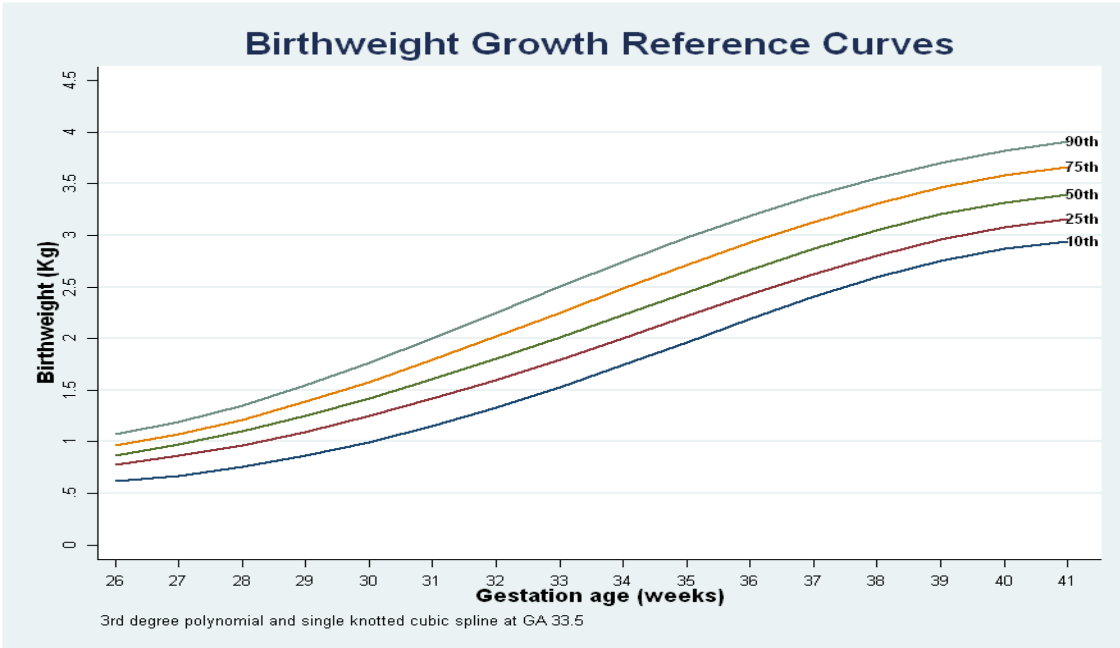


Figure 3: Overall birthweight growth curves of 10th, 25th, 50th, 75th and 90th percentiles for gestational ages of 26 - 41 weeks.

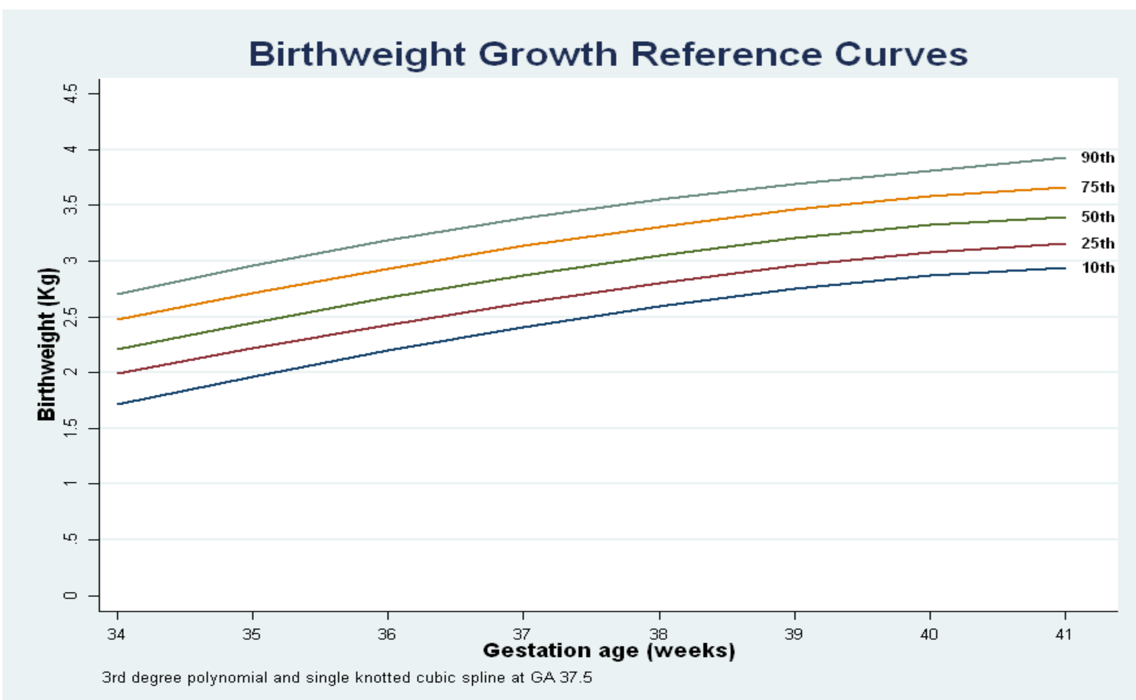


Figure 4: Overall birthweight growth curves of 10th, 25th, 50th, 75th and 90th percentiles for gestational ages of 34 - 41 weeks.

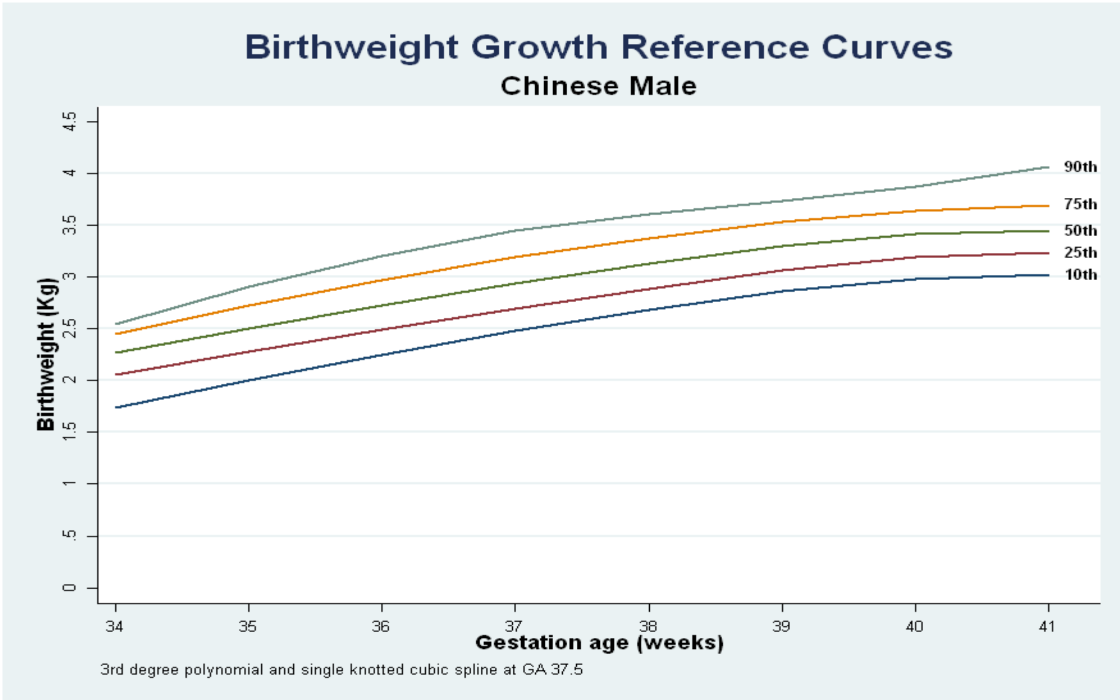


Figure 5: Chinese Male birthweight growth curves of 10th, 25th, 50th, 75th and 90th percentiles for gestational ages of 34 - 41 weeks.

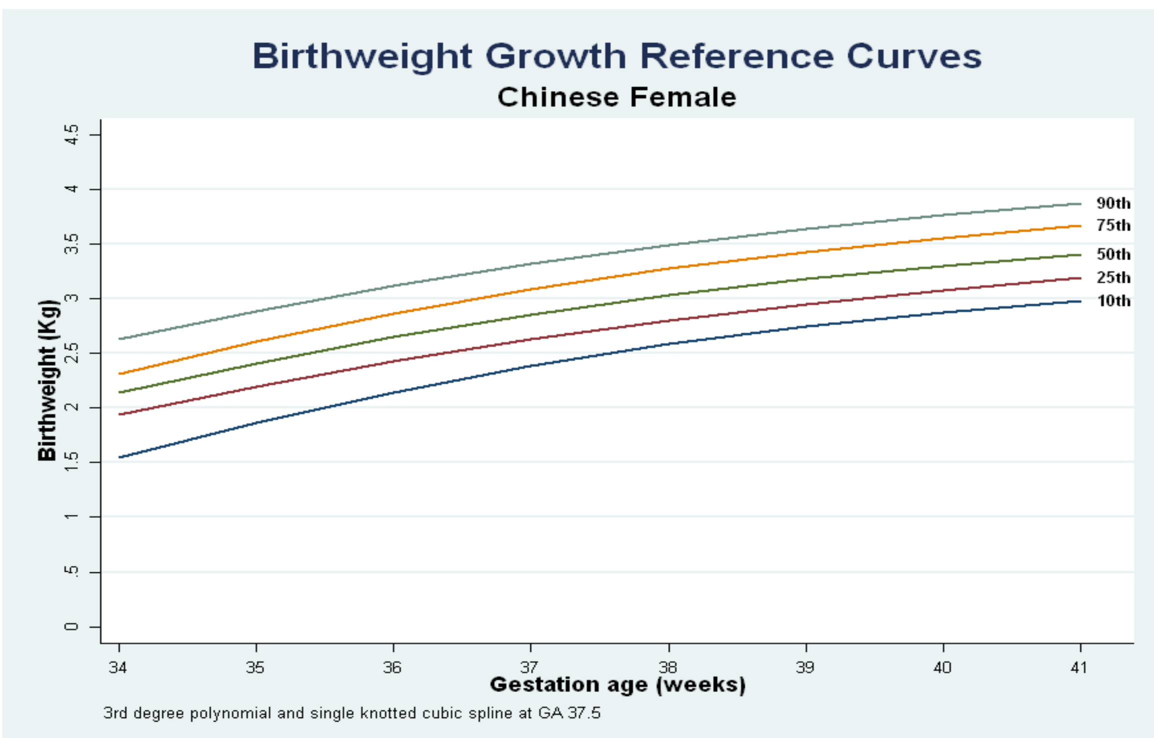


Figure 6: Chinese Female birthweight growth curves of 10th, 25th, 50th, 75th and 90th percentiles for gestational ages of 34 - 41 weeks

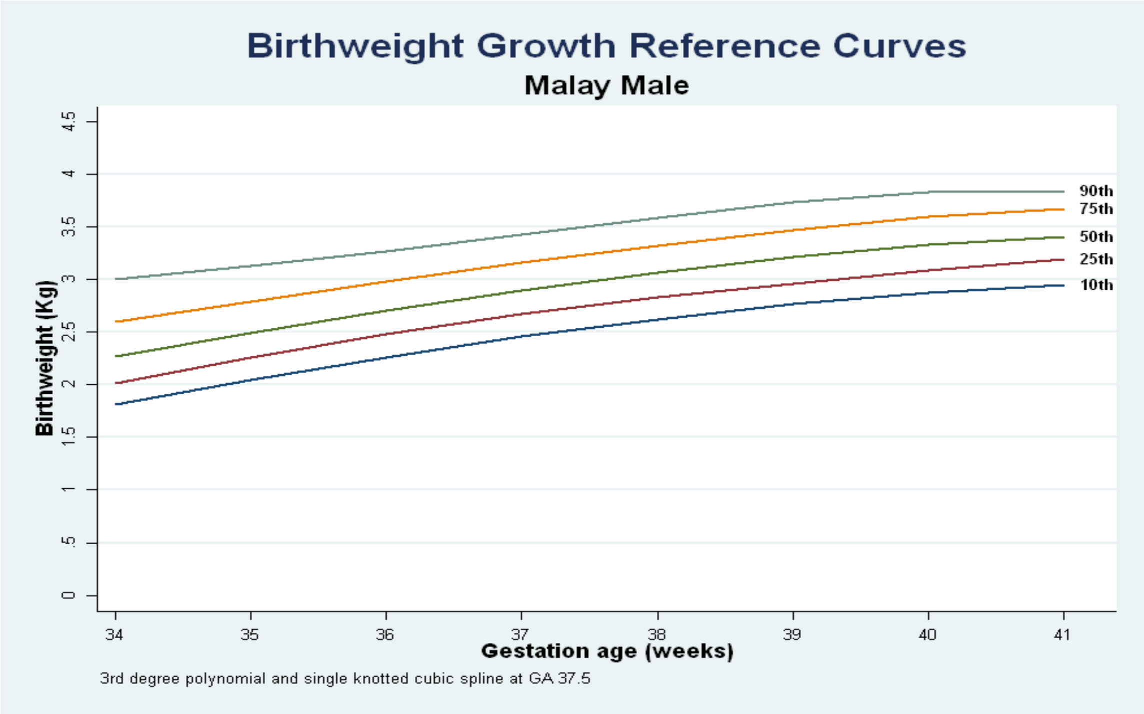


Figure 7: Malay Male birthweight growth curves of 10th, 25th, 50th, 75th and 90th percentiles for gestational ages of 34 - 41 weeks.

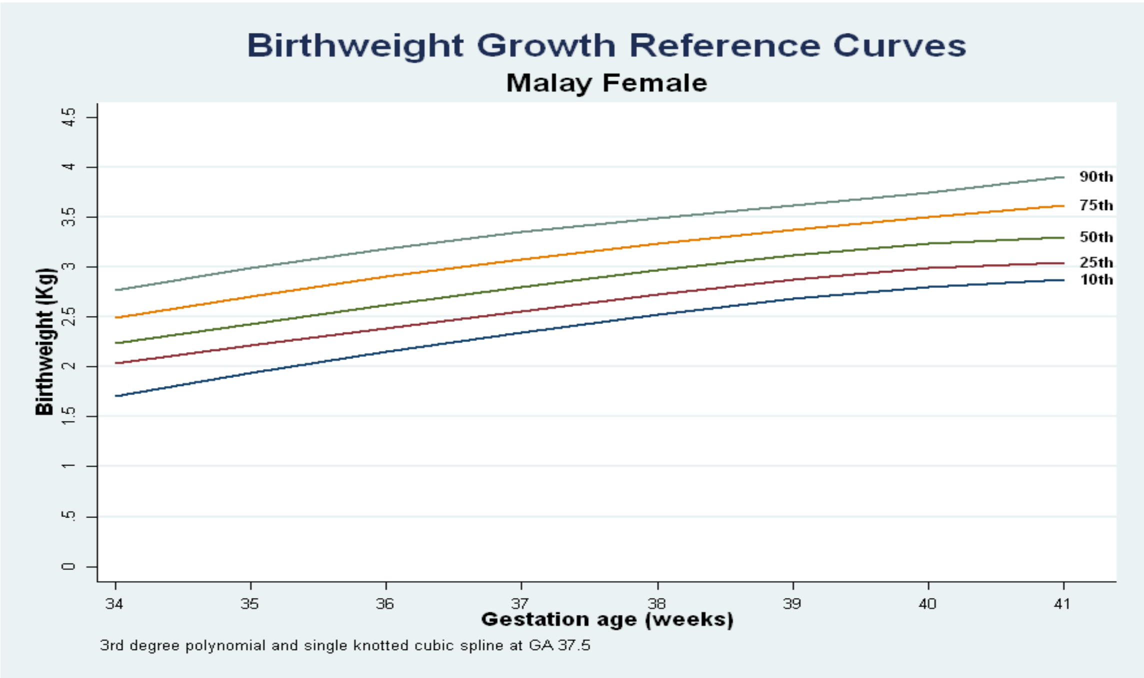


Figure 8: Malay Female birthweight growth curves of 10th, 25th, 50th, 75th and 90th percentiles for gestational ages of 34 - 41 weeks.

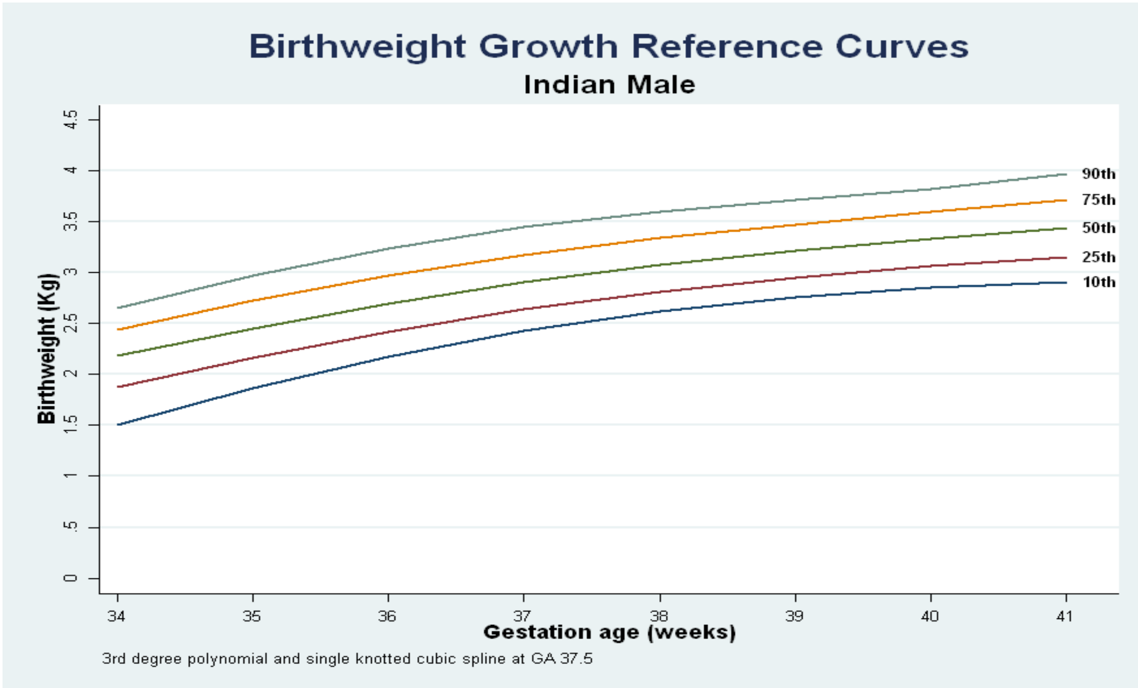


Figure 9: Indian Male birthweight growth curves of 10th, 25th, 50th, 75th and 90th percentiles for gestational ages of 34 - 41 weeks.

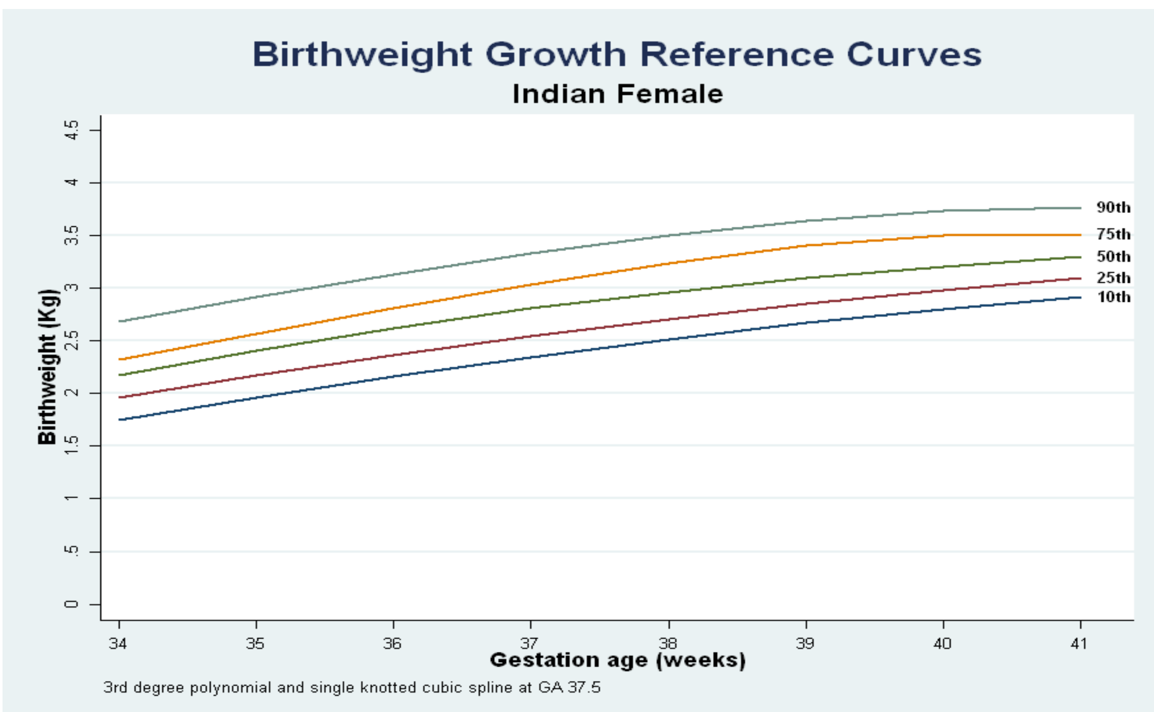


Figure 10: Indian Female birthweight growth curves of 10th, 25th, 50th, 75th and 90th percentiles for gestational ages of 34 - 41 weeks.

4.4 Comparison to Cheng's Birthweight Growth Curves

Graphical overlays (Figures 11 - 13) were used to compare our updated combined gender birthweight curve with that from Cheng et al which has a cohort of 11,026 infants (*Cheng et al, 1972*). In comparison to present data, it appears that Chinese infants in 1972 showed a higher average birthweight between 34 - 37 weeks, though this declined past 37 weeks. In Malay and especially the Indian groups, the average infant birthweight in 1972 was significantly smaller across all gestational stages when compared to present data (Figure 12 & 13).

Tables 15 - 17 show the actual values differences between 1972 and present data for gestational ages from 34 - 41 weeks. The updated birthweight growth curves show more variability in birthweights for the Chinese group (-8.24% to +9.59%). Malay infants are now generally larger than their earlier counterparts (0.90 - 13.76% heavier). This is most evident in the Indian group, with present birthweights exceeding that of their earlier counterparts (1.62 – 28.86% heavier). An exception is seen only at a gestational age of 34 weeks, where the present 10^{th} percentile birthweight is 10.18% less than in 1972. Comparing data obtained approximately 30 years apart, it is evident that the Malay and Indian populations portray much more significant changes in birthweight over this time period, and it will be interesting to consider reasons for this unequal increase.

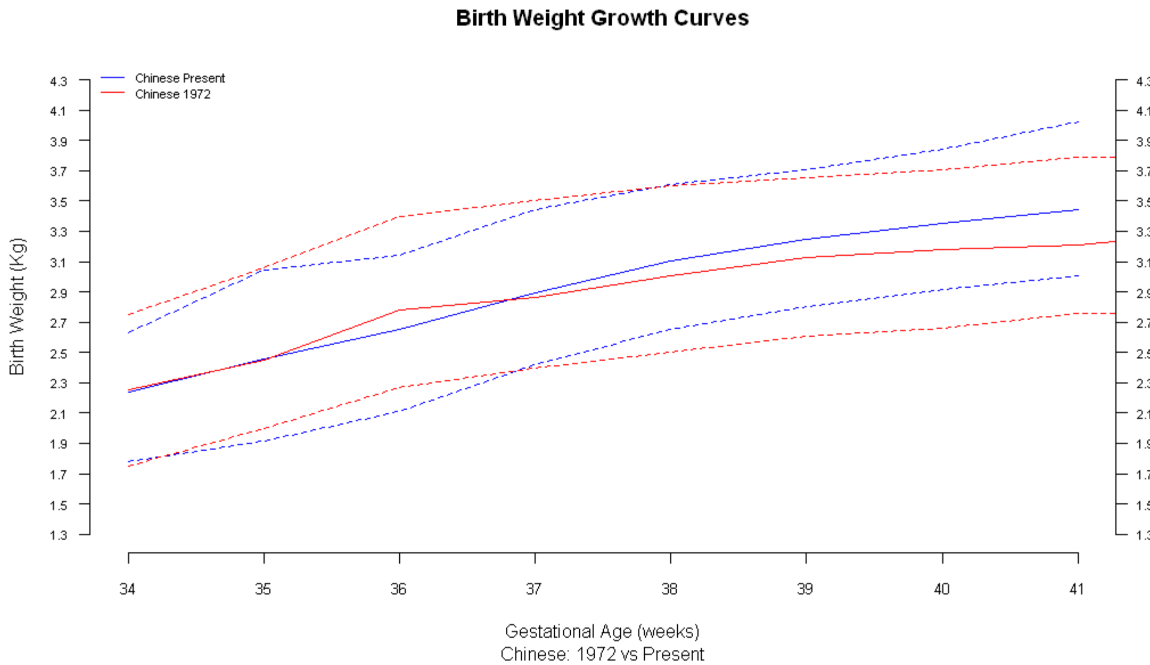


Figure 11: Comparision of Cheng's birthweight growth curves compared to present combined-gender curves for Chinese infants.

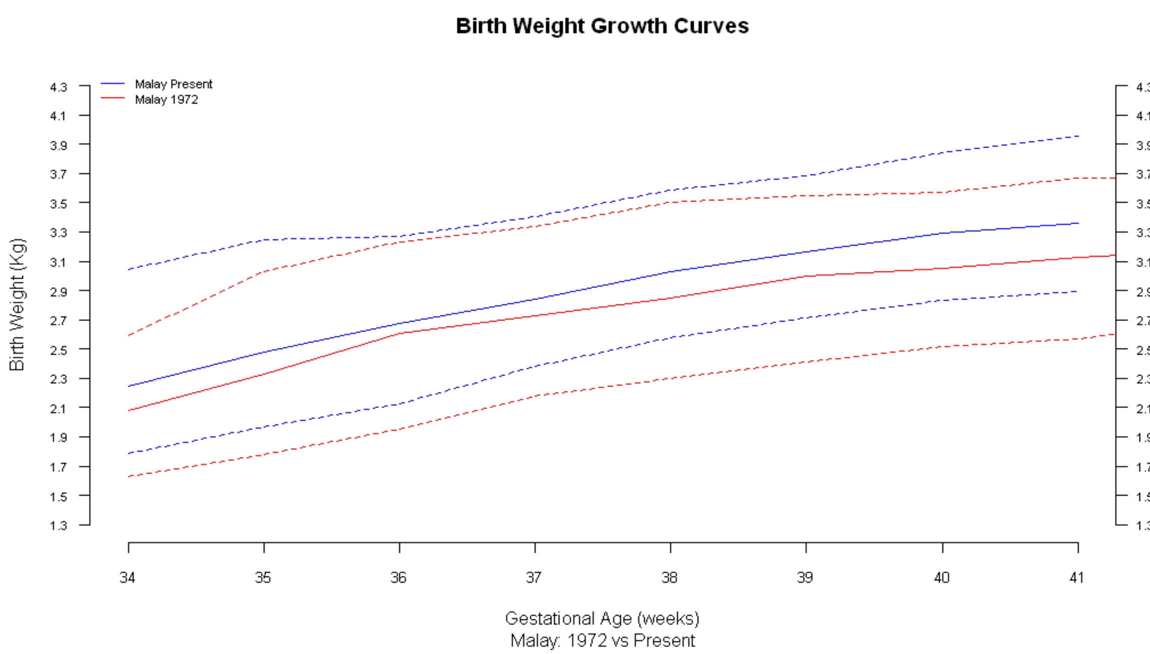


Figure 12: Comparision of Cheng's birthweight growth curves compared to present combined-gender curves for Malay infants.

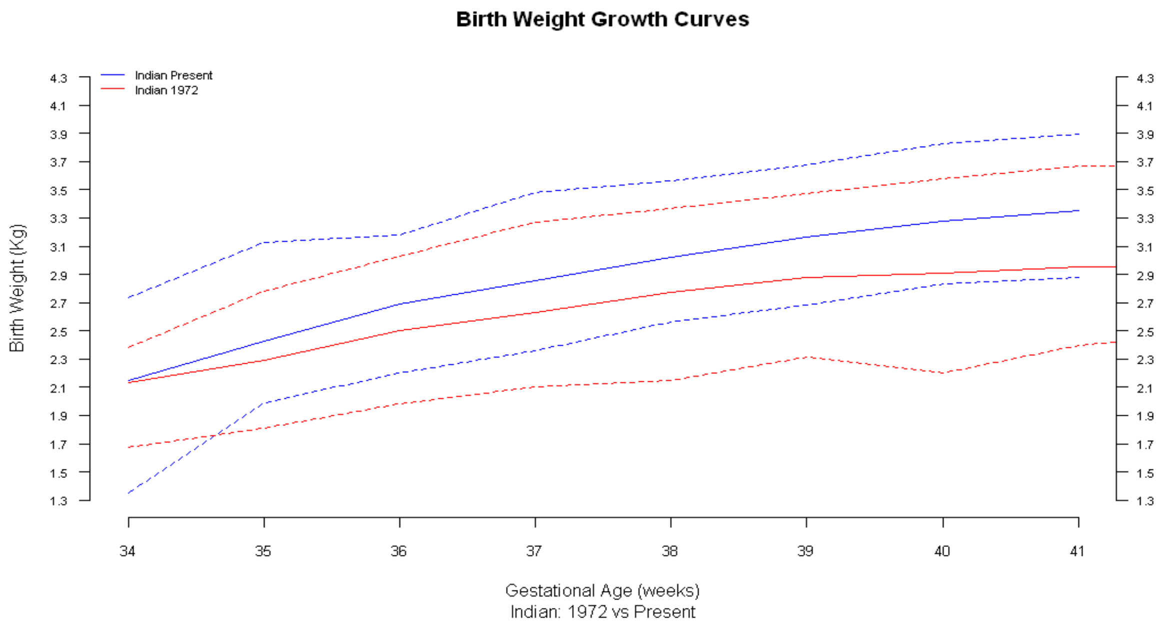


Figure 13: Comparision of Cheng's birthweight growth curves compared to present combined-gender curves for Indian infants.

Gestational Age (weeks)	10th Percentile			50th Percentile			90th Percentile		
	1972	2008	% Δ	1972	2008	% Δ	1972	2008	% Δ
34	1750	1779	1.66%	2250	2218	-1.42%	2750	2575	-6.36%
35	2000	1938	-3.10%	2450	2455	0.20%	3060	3035	-0.82%
36	2270	2175	-4.19%	2780	2655	-4.50%	3400	3120	-8.24%
37	2400	2420	0.83%	2860	2880	0.70%	3500	3390	-3.14%
38	2500	2655	6.20%	3010	3105	3.16%	3600	3590	-0.28%
39	2610	2805	7.47%	3130	3240	3.51%	3650	3690	1.10%
40	2660	2915	9.59%	3180	3354	5.47%	3710	3838	3.44%
41	2760	3015	9.24%	3210	3440	7.17%	3790	3940	3.96%

Table 15: Comparison between 1972 and 2008 birthweight growth curves at 10^{th}, 50^{th} and 90^{th} percentiles for Chinese Infants.

Gestational Age (weeks)	10th Percentile			50th Percentile			90th Percentile		
	1972	2008	% Δ	1972	2008	% Δ	1972	2008	% Δ
34	1630	1810	11.04%	2080	2220	6.73%	2590	2700	4.25%
35	1780	2025	13.76%	2330	2478	6.33%	3030	3150	3.96%
36	1950	2155	10.51%	2610	2673	2.39%	3230	3225	-0.15%
37	2180	2380	9.17%	2730	2840	4.03%	3340	3370	0.90%
38	2300	2575	11.96%	2850	3025	6.14%	3500	3555	1.57%
39	2410	2730	13.28%	3000	3165	5.50%	3550	3670	3.38%
40	2520	2835	12.50%	3050	3295	8.03%	3570	3825	7.14%
41	2690	2920	8.55%	3130	3343	6.79%	3670	3825	4.22%

Table 16: Comparison between 1972 and 2008 birthweight growth curves at 10th, 50th and 90th percentiles for Malay Infants.

Gestational Age (weeks)	10th Percentile			50th Percentile			90th Percentile		
	1972	2008	% Δ	1972	2008	% Δ	1972	2008	% Δ
34	1670	1500	-10.18%	2130	2165	1.62%	2380	2700	13.45%
35	1810	2044	12.93%	2290	2425	5.90%	2780	2930	5.40%
36	1980	2200	11.11%	2500	2690	7.60%	3030	3140	3.63%
37	2100	2360	12.38%	2630	2853	8.46%	3270	3415	4.43%
38	2150	2570	19.53%	2770	3020	9.03%	3370	3555	5.49%
39	2310	2690	16.45%	2880	3163	9.81%	3470	3665	5.62%
40	2200	2835	28.86%	2910	3280	12.71%	3580	3820	6.70%
41	2400	2890	20.42%	2950	3350	13.56%	3670	3880	5.72%

Table 17: Comparison between 1972 and 2008 birthweight growth curves at 10th, 50th and 90th percentiles for Indian Infants.

4.5 Gender Analysis

In agreement with studies conducted in other populations, significant differences were found in mean birthweight between male and female infants in this study (Kramer et al., 1990) (*Storms and Van Howe., 2004*) (*Hindmarsh et al., 2002*). The birthweight of male infants were statistically higher than that of the female infants by 93.7 g ($P < 0.001$) as seen in Mixed Modeling (Table 28). Table 18 below shows the comparison of mean birthweight by gestational age between genders. The mean difference found between the two genders ranged from 2.25% to 4.28% depending on gestational age, and found to be significant by *t-test*. The mean birthweight for gestational ages 36 - 41 weeks between the two genders was found to be statistically significant (P <0.001).

Gestational Age (weeks)	Male Birthweight		Female Birthweight		Mean Difference		
	Mean	± SD	Mean	± SD	Δ	% Δ	P-value*
34	2243.9	382.7	2178.5	345.6	65.41	3.00%	0.199
35	2536.2	410.2	2471.4	438.2	64.79	2.62%	0.144
36	2719.7	390.7	2608.2	386.0	111.55	4.28%	0.000
37	2916.5	379.8	2834.0	380.2	82.46	2.91%	0.000
38	3117.9	374.2	3025.1	362.6	92.72	3.06%	0.000
39	3257.5	350.4	3157.8	359.9	99.71	3.16%	0.000
40	3383.4	369.7	3289.4	363.3	94.00	2.86%	0.000
41	3451.4	363.8	3375.3	360.4	76.05	2.25%	0.002

*Statistical significance of *t*-test

Table 18: Mean birthweight comparison by gender and gestational age.

Male and female infant birthweight growth curves were overlaid as shown (Figure 14) to highlight the differences between genders. Table 19 has been created to compare points on the birthweight growth curves at gestational ages from 34 - 41 weeks. Based on the smoothed birthweight curves, male infants were found to have larger birthweight ranging from 1.71% - 10.76% depending on gestational age, with a sole exception at the 90th percentile of a 35 week gestation, where males are smaller by 0.8%.

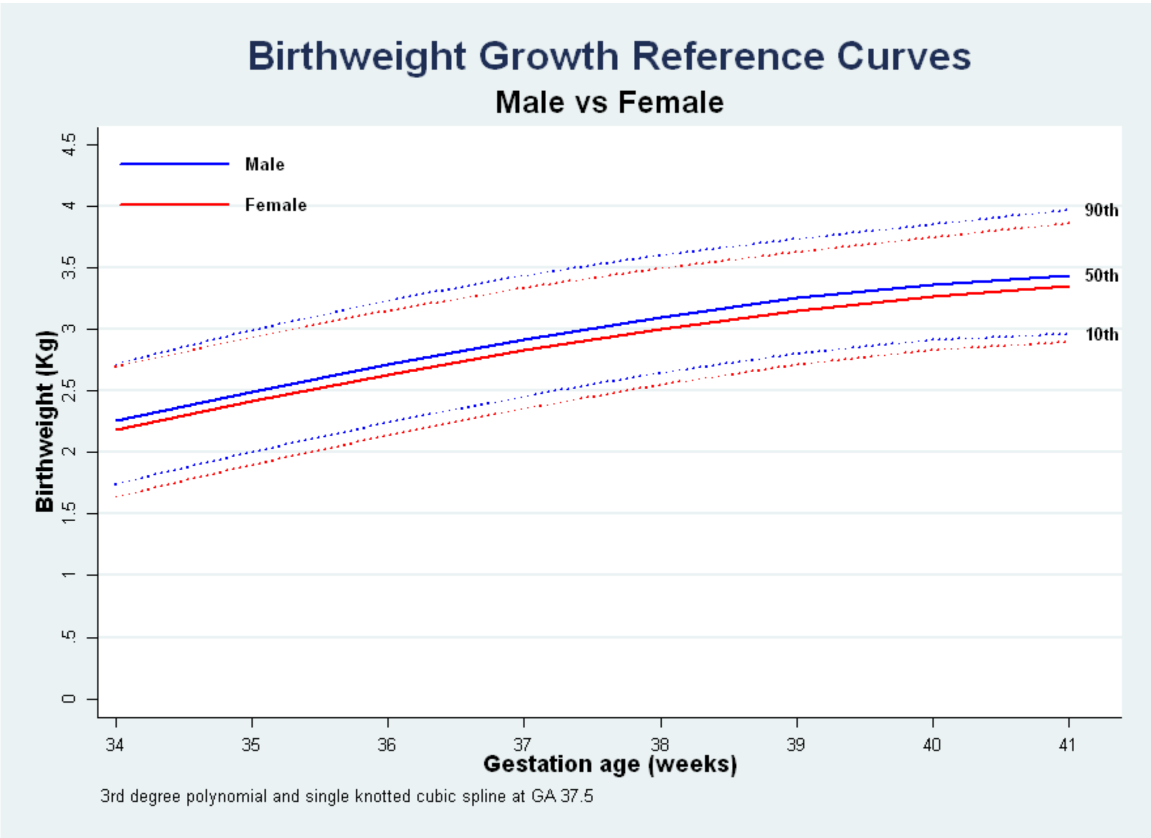


Figure 14: Birthweight growth curves of 10th, 50th and 90th percentile for Male (Blue) and Female (Red) infants for gestational age of 34 - 41 weeks.

Gestational Age (weeks)	10th Percentile			50th Percentile			90th Percentile		
	Male	Female	% Δ	Male	Female	% Δ	Male	Female	% Δ
34	1743	1787	-2.46%	2265	2180	3.90%	2675	2630	1.71%
35	2090	1887	10.76%	2495	2450	1.84%	3105	3130	-0.80%
36	2208	2095	5.39%	2720	2600	4.62%	3215	3140	2.39%
37	2460	2345	4.90%	2905	2820	3.01%	3425	3333	2.78%
38	2650	2570	3.11%	3110	3015	3.15%	3615	3510	2.99%
39	2800	2700	3.70%	3255	3145	3.50%	3715	3620	2.62%
40	2910	2835	2.65%	3370	3265	3.22%	3875	3758	3.11%
41	2970	2906	2.20%	3435	3365	2.08%	3955	3855	2.59%

Table 19: Mean birthweight comparison between male and female 10th, 50th and 90th percentiles at gestational age from 34 - 41 weeks.

4.6 Ethnic Group Analysis

Analysis between ethnic groups was done to determine the contribution, if any, of this factor to infant birthweight. This analysis was performed on the three main ethnic groups in Singapore – Chinese, Malays and Indians. 1021 infants with unknown ethnicity, or ethnicities outside these three defined groups were a minority 4.7% of the original record number, and were excluded from this study.

Between the three ethnic groups considered, significant differences in the mean birthweight were identified by mixed model analysis (Table 28). Chinese infants were the heaviest with a statistically significant difference of 38.3 g and 53.2 g in birthweight when compared to Malay and Indian infants, respectively ($P < 0.001$).

In concordance with the combined gender birthweight growth curve for the three ethnic group (Figure 15), Chinese infants have higher birthweight as compared to Malay and Indian across three percentile range of 10^{th}, 50^{th} and 90^{th} for gestational age of 37 weeks onwards. Malay and Indian infants have similar birthweight across the three percentile range from gestational age of 37 weeks onwards. The sample size for preterm infants (<37 weeks gestational age) was small and therefore portray a more sparse distribution.

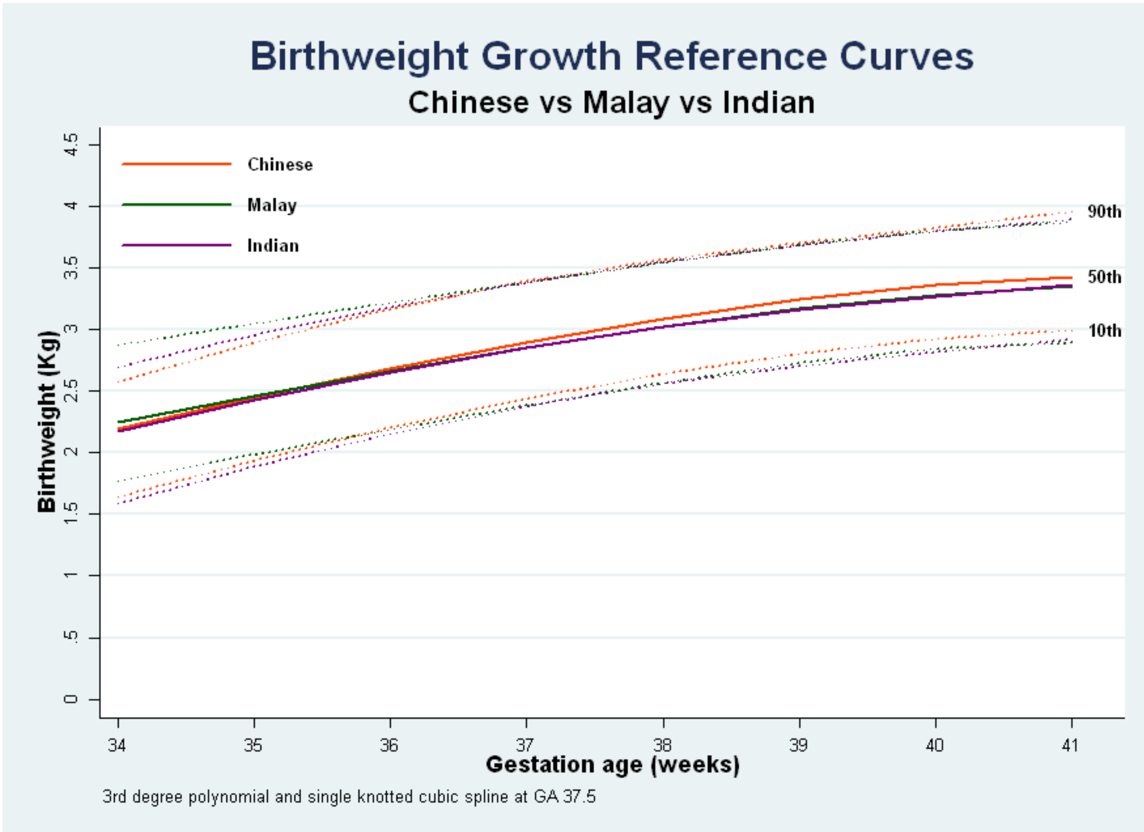


Figure 15: Birthweight growth curves for Chinese (Red), Malay (Green) and Indian (Purple) infants.

Further analysis on the contribution of gender and ethnicity was done by creating three more separate birthweight growth curves (Figures 16 - 18). These curve illustrate that in all ethnicities considered, males were heavier than females at birth. Chinese and Malay male infants were consistently larger than female counterparts respectively. In Indians, the percentile differences between the two genders were more drastic, with Indian females observed to be slightly larger than male infants at gestational ages between 34 to 36 weeks at the 10^{th} percentile.

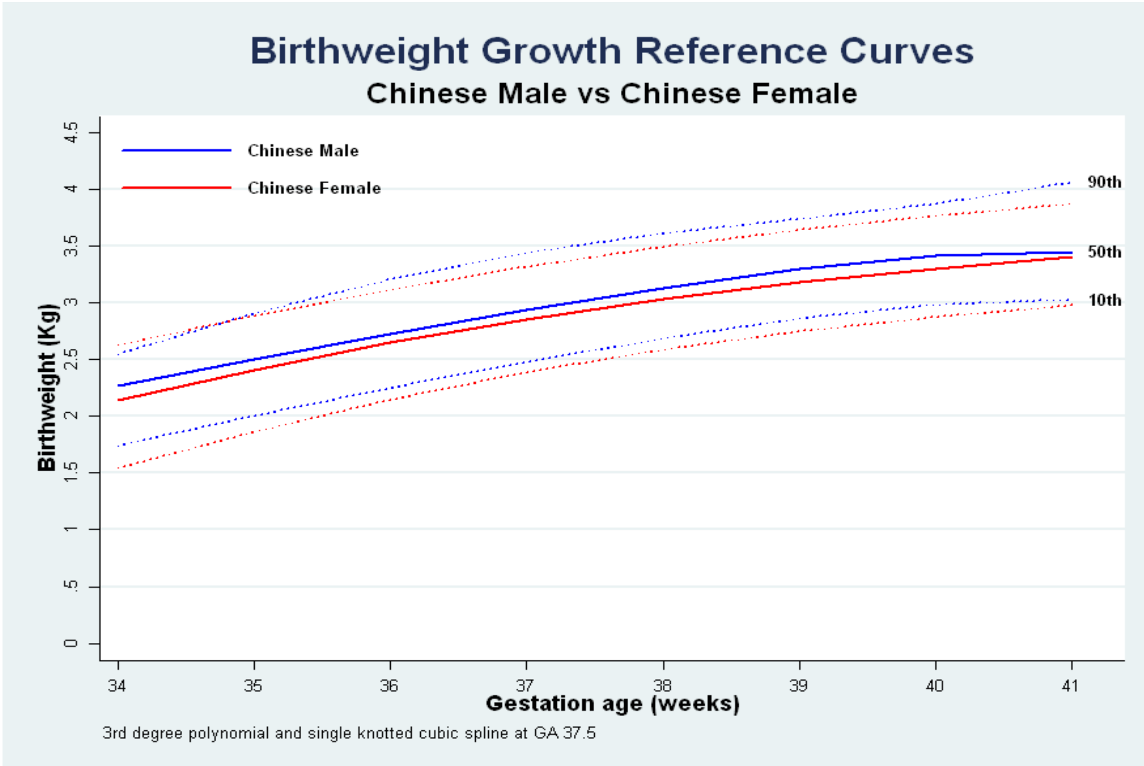


Figure 16: Birthweight growth curves for Chinese male and Chinese female infants.

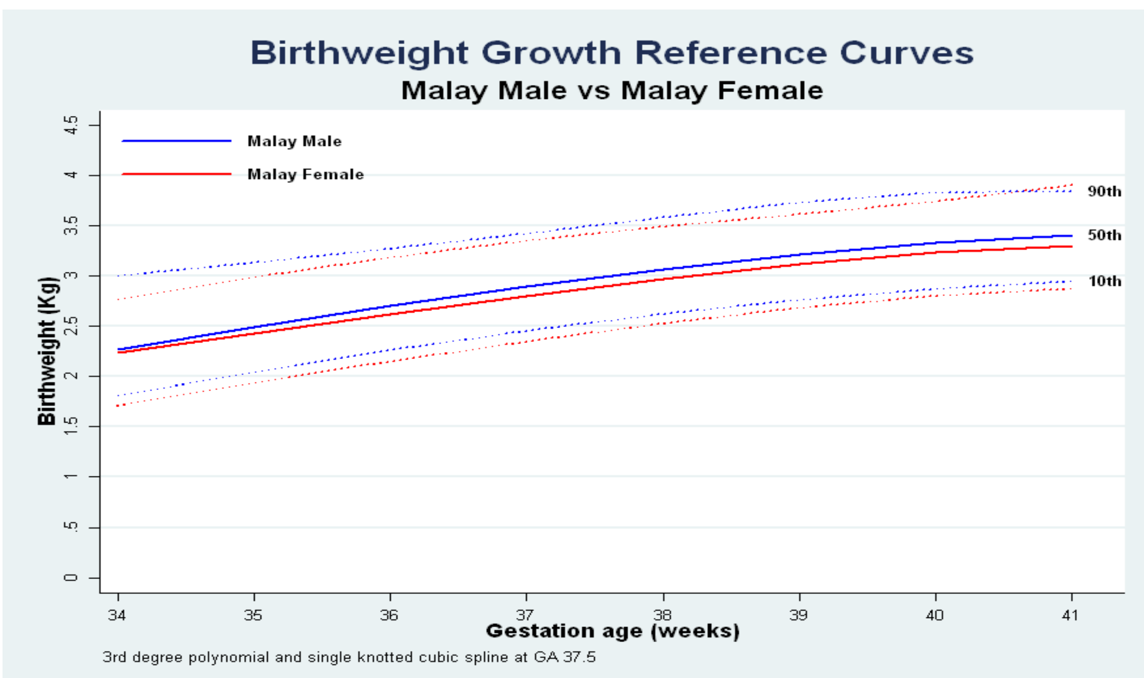


Figure 17: Birthweight growth curves for Malay male and Malay female infants.

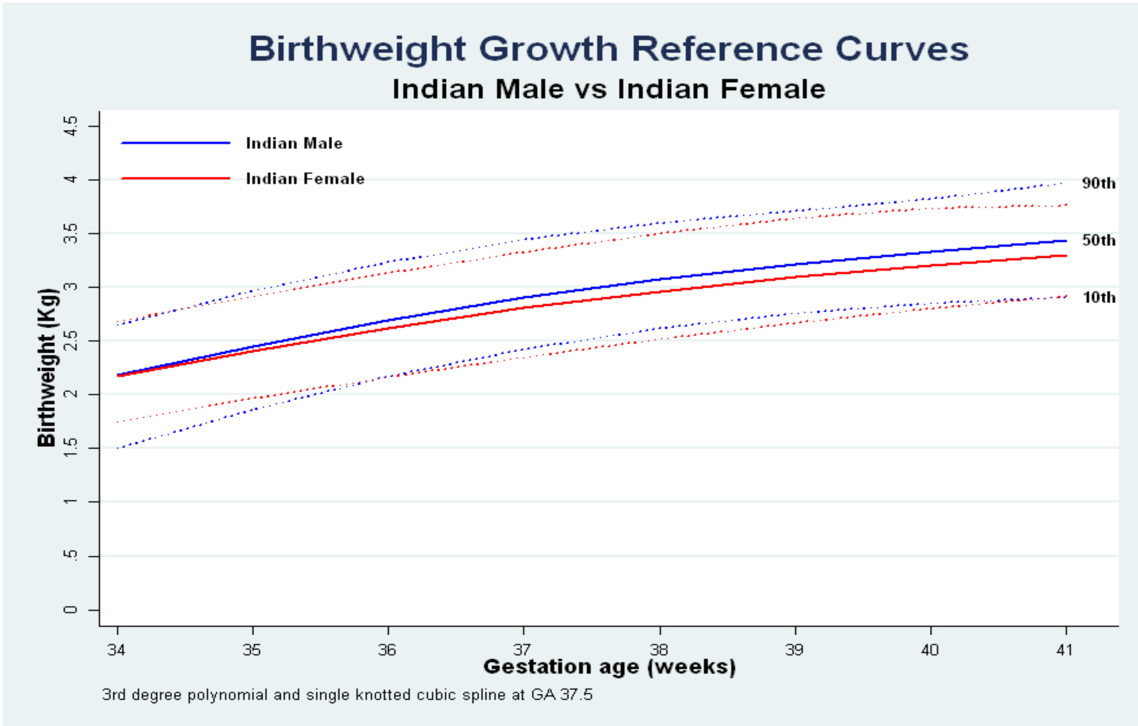


Figure 18: Birthweight growth curves for Indian male and Indian female infants.

Two more birthweight growth curves (Figure 19 & 20) were created to make comparison among the three ethnic groups by gender. From gestational age of 37 weeks onwards, Chinese males were on the average, heavier than their Malay and Indian counterparts. At an earlier window between 34 - 37 gestational weeks, Malay males appear to be the predominant heavyweights (Figure 19). In females, no distinct differences were observed between the ethnicities.

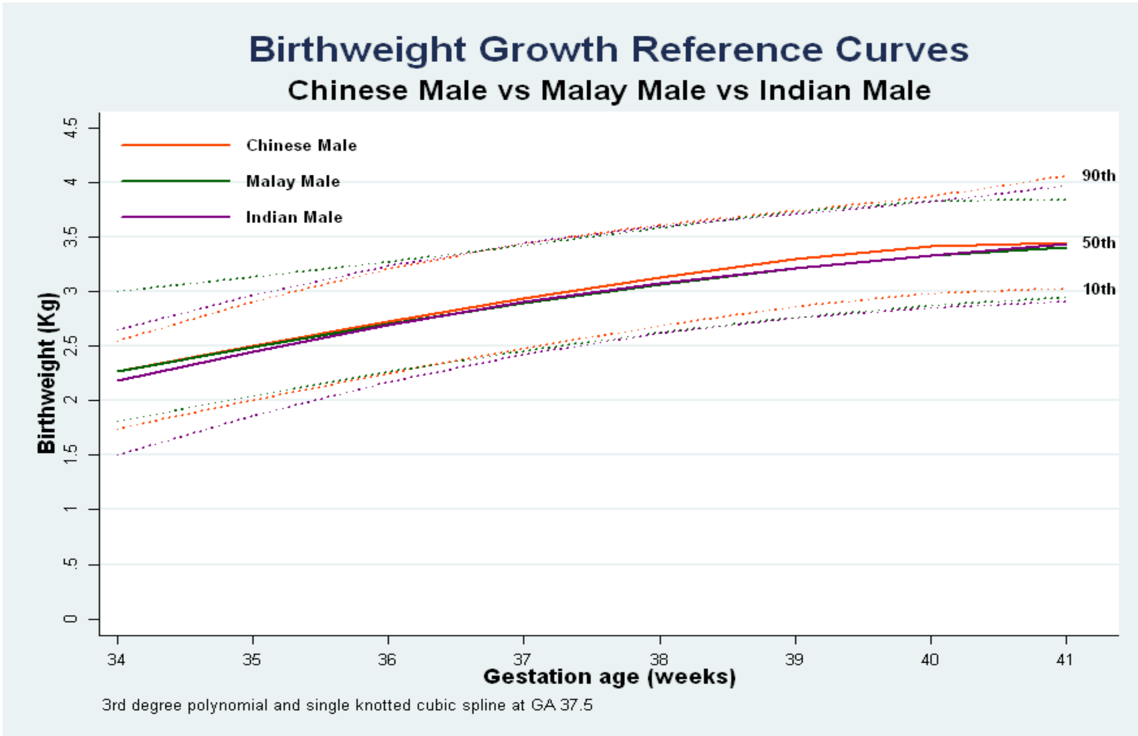


Figure 19: Birthweight growth curves for male infants among the 3 ethnic groups.

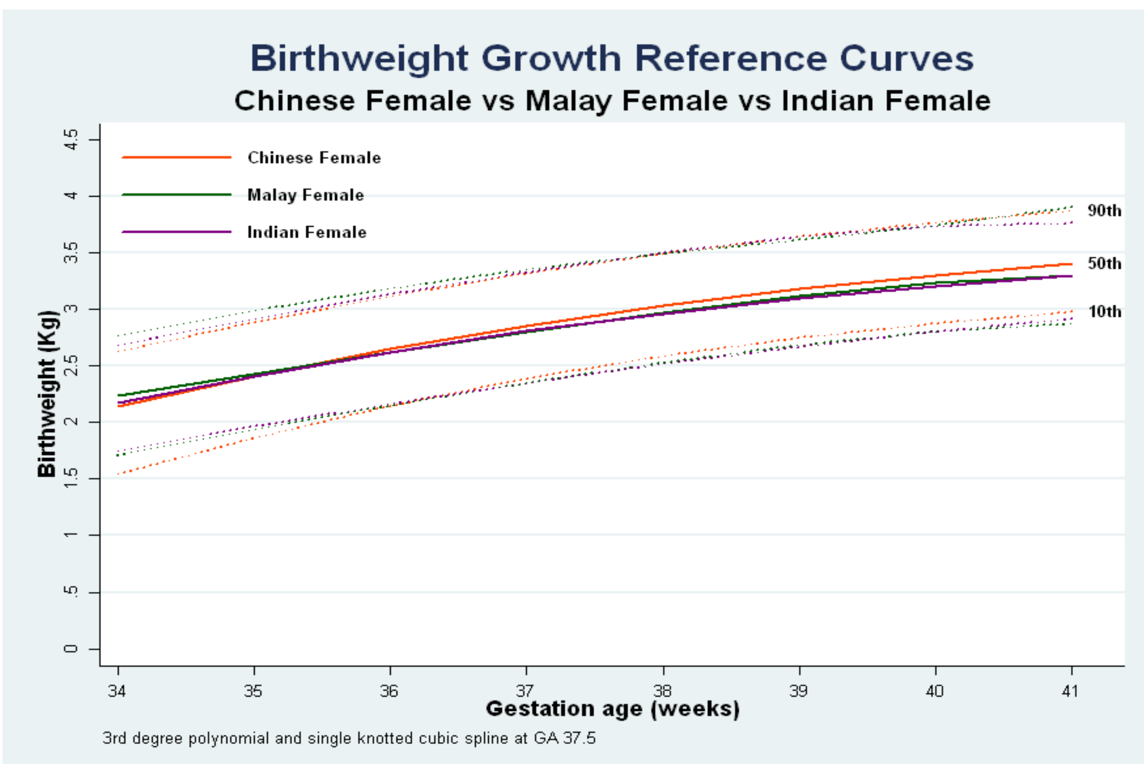


Figure 20: Birthweight growth curves for female infants among the 3 ethnic groups.

Tables 20 - 22 show the mean birthweight of the three ethnic groups by gestational age. Birthweights of Malay and Indian infants were compared to Chinese infants. Table 20 presents the overall infant birthweight by gestational age and ethnic groups, without stratification by gender. Overall comparison shows that statistical significance differences in mean birthweight among the three ethnic groups can only be observed at gestational age of 38 - 41 weeks.

Table 21 shows that statistically significant differences in mean birthweight were observed when comparing male infants among the three ethnic groups for gestational age of 37 to 41 weeks. The average mean difference in birthweight between ethnic groups for male infants, depending on gestational age ranges from -2.12% to +2.87% for comparison between Chinese and Malay; -2.98% to +9.83% for comparison between Chinese and Indian.

Statistically significant differences in mean birthweight of female infants among the three ethnic groups were observed at gestational age of 38 - 41 weeks (Table 22). These differences were marginal when compared to the differences between male infants of various ethnicities. The average mean difference in birthweight between ethnic groups for female infants, depending on gestational age ranges from -4.56% to +2.69% for comparison between Chinese and Malay; -6.22% to 4.59% for comparison between Chinese and Indian.

Gestational Age (weeks)	Indian			Malay			Chinese		
	Mean	± SD	% Δ	Mean	± SD	% Δ	Mean	± SD	P-value*
34	2138.2	461.8	2.56%	2254.1	368.5	-2.72%	2192.9	315.3	0.242
35	2430.9	391.9	3.05%	2532.7	438.2	-1.09%	2505.0	414.9	0.265
36	2663.7	372.9	-0.68%	2683.6	411.5	-1.41%	2645.7	375.2	0.447
37	2874.0	397.8	0.86%	2861.0	381.9	1.32%	2898.6	372.6	0.086
38	3037.4	389.0	2.35%	3049.1	375.3	1.95%	3108.7	357.9	<0.001
39	3168.4	367.1	2.47%	3179.5	368.2	2.12%	3246.7	343.7	<0.001
40	3302.3	375.4	1.98%	3308.2	381.4	1.80%	3367.6	355.9	<0.001
41	3363.1	370.3	3.12%	3373.7	370.2	2.80%	3468.1	348.6	0.001

*Overall comparison, statistical significance of ANOVA

Table 20: Overall infant birthweight by gestational age and ethnic groups.

Gestational Age (weeks)	Indian			Malay			Chinese		
	Mean	± SD	% Δ	Mean	± SD	% Δ	Mean	± SD	P-value*
34	2069.3	501.6	9.83%	2285.3	376.8	-0.55%	2272.7	295.3	0.079
35	2467.2	408.4	2.39%	2572.7	436.4	-1.81%	2526.2	373.9	0.392
36	2761.0	362.5	-2.98%	2736.6	417.6	-2.12%	2678.7	365.3	0.223
37	2923.4	399.5	0.83%	2885.4	368.0	2.16%	2947.6	379.0	0.027
38	3079.3	402.3	2.25%	3099.8	378.8	1.57%	3148.4	355.9	<0.001
39	3211.0	351.7	2.88%	3220.4	365.0	2.58%	3303.5	332.6	<0.001
40	3370.6	388.4	1.28%	3346.8	383.9	2.00%	3413.8	350.1	<0.001
41	3398.3	388.2	3.26%	3411.1	349.6	2.87%	3508.9	358.0	0.017

*Overall comparison, statistical significance of ANOVA

Table 21: Male infant birthweight by gestational age and ethnic groups.

Gestational Age (weeks)	Indian			Malay			Chinese		
	Mean	± SD	% Δ	Mean	± SD	% Δ	Mean	± SD	P-value*
34	2253.1	378.6	-6.22%	2214.0	357.5	-4.56%	2113.0	318.0	0.305
35	2366.6	360.8	4.59%	2493.6	438.7	-0.74%	2475.3	468.7	0.474
36	2563.8	359.0	1.72%	2625.5	397.8	-0.68%	2607.8	384.2	0.510
37	2815.6	388.6	1.11%	2831.1	396.7	0.55%	2846.8	358.9	0.565
38	2993.1	369.7	2.40%	2993.2	363.4	2.39%	3064.8	355.2	<0.001
39	3120.4	378.5	2.14%	3136.9	366.9	1.60%	3187.1	345.3	<0.001
40	3241.6	353.1	2.47%	3270.0	375.2	1.58%	3321.6	355.8	0.001
41	3327.6	350.0	3.02%	3338.5	386.3	2.69%	3428.2	335.5	0.029

*Overall comparison, statistical significance of ANOVA

Table 22: Female infant birthweight by gestational age and ethnic groups

Tables 23 - 25 show the mean birthweight of the three ethnic groups by gestational age adjusted for maternal age, parity and diabetes. Adjusted P-values were presented in comparison with birthweights of Malay and Indian infants to Chinese infants. Table 23 presents the overall infant birthweight by gestational age and ethnic groups adjusted for maternal age, parity and diabetes, without stratification by gender. Overall comparison shows that statistical significance differences in mean birthweight among the three ethnic groups can be observed at gestational age of 38 - 41 weeks even after adjustment.

Table 24 shows that statistically significant adjusted P-values can be observed for gestational age of 39 and 40 weeks for comparison between Chinese and Malay; gestational age of 38 and 39 weeks for comparison between Chinese and Indian. The average mean difference in birthweight between ethnic groups for male infants, depending on gestational age ranges from -2.16% to +2.79% for comparison between Chinese and Malay; -3.07% to +8.95% for comparison between Chinese and Indian.

Statistically significant differences in mean birthweight of female infants among the three ethnic groups were observed at gestational age of 38 - 40 weeks (Table 25). The average mean difference in birthweight between ethnic groups for female infants, depending on gestational age ranges from -4.78% to +2.62% for comparison between Chinese and Malay; -6.63% to 4.39% for comparison between Chinese and Indian.

Gestational Age (weeks)	Indian			Malay			Chinese		Adjusted P-values	
	Mean	SD	% Δ	Mean	SD	% Δ	Mean	SD	Chinese vs Malay	Chinese vs Indian
34	2138.2	461.8	2.49	2254.1	368.5	-2.79	2192.9	315.3	0.665	0.317
35	2430.9	391.9	2.96	2532.7	438.2	-1.11	2505.0	414.9	0.757	0.217
36	2663.7	372.9	-0.68	2683.6	411.5	-1.43	2645.7	375.2	0.404	0.960
37	2874.0	397.8	0.85	2861.0	381.9	1.30	2898.6	372.6	0.179	0.279
38	3037.4	389.0	2.29	3049.1	375.3	1.92	3108.7	357.9	0.000	<0.001
39	3168.4	367.1	2.41	3179.5	368.2	2.07	3246.7	343.7	0.000	<0.001
40	3302.3	375.4	1.94	3308.2	381.4	1.76	3367.6	355.9	0.000	<0.001
41	3363.1	370.3	3.03	3373.7	370.2	2.72	3468.1	348.6	0.012	0.008

Table 23: Overall infant birthweight by gestational age and ethnic groups after adjusted for maternal age, parity and diabetes.

Gestational Age (weeks)	Indian			Malay			Chinese		Adjusted P-values	
	Mean	SD	% Δ	Mean	SD	% Δ	Mean	SD	Chinese vs Malay	Chinese vs Indian
34	2069.3	501.6	8.95%	2285.3	376.8	-0.56%	2272.7	295.3	0.929	0.030
35	2467.2	408.4	2.34%	2572.7	436.4	-1.84%	2526.2	373.9	0.857	0.384
36	2761.0	362.5	-3.07%	2736.6	417.6	-2.16%	2678.7	365.3	0.143	0.190
37	2923.4	399.5	0.82%	2885.4	368.0	2.11%	2947.6	379.0	0.060	0.551
38	3079.3	402.3	2.20%	3099.8	378.8	1.54%	3148.4	355.9	0.092	0.002
39	3211.0	351.7	2.80%	3220.4	365.0	2.51%	3303.5	332.6	0.000	<0.001
40	3370.6	388.4	1.27%	3346.8	383.9	1.96%	3413.8	350.1	0.001	0.119
41	3398.3	388.2	3.15%	3411.1	349.6	2.79%	3508.9	358.0	0.080	0.051

Table 24: Male infant birthweight by gestational age and ethnic groups after adjusted for maternal age, parity and diabetes

Gestational Age (weeks)	Indian			Malay			Chinese		Adjusted P-values	
	Mean	**SD**	**% Δ**	**Mean**	**SD**	**% Δ**	**Mean**	**SD**	**Chinese vs Malay**	**Chinese vs Indian**
34	2253.1	378.6	-6.63%	2214.0	357.5	-4.78%	2113.0	318.0	0.998	0.473
35	2366.6	360.8	4.39%	2493.6	438.7	-0.74%	2475.3	468.7	0.651	0.470
36	2563.8	359.0	1.69%	2625.5	397.8	-0.68%	2607.8	384.2	0.746	0.140
37	2815.6	388.6	1.10%	2831.1	396.7	0.55%	2846.8	358.9	0.923	0.197
38	2993.1	369.7	2.34%	2993.2	363.4	2.34%	3064.8	355.2	<0.001	0.001
39	3120.4	378.5	2.09%	3136.9	366.9	1.58%	3187.1	345.3	0.044	0.004
40	3241.6	353.1	2.41%	3270.0	375.2	1.55%	3321.6	355.8	0.031	0.002
41	3327.6	350.0	2.94%	3338.5	386.3	2.62%	3428.2	335.5	0.135	0.061

Table 25: Female infant birthweight by gestational age and ethnic groups after adjusted for maternal age, parity and diabetes.

4.7 Trend Over Time

Linear regression was used to evaluate trends for some of the variables collected in the data set. A statistically significant decrease in birthweight of 7.7 g per year over the period of data collection (P for Trend = 0.0138) was noted. Primiparous births have increased linearly by 1.0% every year (P for Trend <0.001). However, incidences of diabetes and low birth weight cases did not have any significant changes over the 8-year period of data collection.

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	P for trend
Birthweight (g)	3106.4	3075.4	3090.1	3117.8	3097.5	3064.9	3061.9	3056.3	3032.5	0.0138
Primiparous (%)	34.0%	36.5%	37.1%	38.5%	38.9%	40.2%	40.9%	41.9%	42.2%	0.0000
Low Birth Weight <= 2500 g (%)	7.9%	10.2%	9.7%	8.3%	9.7%	10.5%	9.5%	10.6%	10.6%	0.0578
Diabetes (%)	6.3%	7.6%	7.3%	5.9%	7.1%	5.9%	8.8%	8.2%	9.5%	0.0613

Table 26: The rate of primiparity, low birthweight, incidences of maternal diseases (diabetes) and mean birthweight by year.

4.8 Maternal Factors Analysis

Results for the mean birthweight differences among the categories of variables are shown in Table 27. Statistically significant differences in mean birthweight between categories of variables (maternal age, parity, diabetes, hypertension and ART pregnancy) were observed (P <0.001). However, no statistically significant result in mean birthweight was found between mother with and without anemia.

Results from the mixed-model analysis are presented in Table 28. Chinese infants are the heaviest, with a statistically significant difference of 38.3 g and 53.2 g in birthweight when compared to Malay and Indian infants, respectively (P < 0.001). The birthweight of males were statistically higher than that of the females by 93.7 g (P < 0.001). We also observed a gradual trend of increasing birthweight with advancing maternal age until the age of 40 years. The youngest mothers sampled (20 year old group), generally gave birth to lighter infants than older maternal age groups (>20 year old onwards) (P < 0.001). The magnitude of the increment in birthweight among maternal age groups fell progressively after 41 years old. Primiparous women generally gave birth to lighter infants, compared with multiparous women (P < 0.001). The increasing birthweight can be seen from the first to third births, with a minimal decline from the fourth baby onwards. With respect to maternal disease categories, statistically significant differences were observed in infant birthweights between mothers with and without gestational diabetes and hypertension (P < 0.001). However, the presence of anaemia in mothers did not have a statistically significant effect on infant birthweight. (P = 0.390). Birthweights of singleton infant conceived by ART were 46.2 g smaller than spontaneously-conceived peers. However, the difference in birthweight between these two groups of infants were not statistically significant (P = 0.065).

		Mean	**± SD**	**P-value***
Maternal age	< 20 yrs	2860.007	484.3216	< 0.0001
	21 - 25 yrs	3010.714	459.6753	
	26 - 30 yrs	3076.944	471.7006	
	31 - 35 yrs	3118.844	492.9915	
	36 - 40 yrs	3131.624	513.9848	
	> 41 yrs	3033.431	580.5393	
Parity	0	3032.902	499.867	< 0.0001
	1	3105.43	482.1477	
	2	3115.592	475.0226	
	3	3098.812	497.9797	
	4 or more	3087.793	493.7457	
Diabetes	No	3073.547	491.5388	< 0.0001
	Yes	3132.966	475.8896	
Anemia	No	3078.272	490.9997	0.3871
	Yes	3051.944	458.6594	
Hypertension	No	3085.217	479.8751	< 0.0001
	Yes	2891.412	688.1474	
ART Pregnancy	No	3080.063	487.2503	0.0001
	Yes	2879.777	717.7	

Table 27: Mean birthweight for maternal factors that affecting birthweight.

		95% CI		
	B	**LB**	**UB**	**P-value**
Gestation (weeks)	172.5	169.7	175.3	<0.001
Malay	-38.3	-51.8	-24.8	<0.001
Indian	-53.2	-68.2	-38.3	<0.001
Female	-93.7	-103.5	-84.0	<0.001
21-25 yrs	44.0	17.2	70.8	0.001
26-30 yrs	72.2	45.7	98.6	<0.001
31-35 yrs	112.0	84.6	139.5	<0.001
36-40 yrs	130.4	100.8	160.1	<0.001
>41 yrs	73.0	30.6	115.4	0.001
Parity 1	63.9	52.6	75.1	<0.001
Parity 2	76.8	61.4	92.1	<0.001
Parity 3	77.0	54.6	99.5	<0.001
Parity 4 or more	75.5	42.3	108.7	<0.001
Diabetes	78.7	59.4	98.1	<0.001
Anemia	19.6	-25.1	64.4	0.390
Hypertension	-49.4	-75.7	-23.2	<0.001
ART Pregnancy	-46.2	-95.3	2.9	0.065

LB: Lower bound; UB: Upper bound

[1]Reference: Chinese
[2]Reference: <20 years old
[3]Reference: Parity = 0

Table 28: Factors affecting birthweight in singleton newborns from Year 2000 – 2008.

CHAPTER 5 DISCUSSION

5.1 Birthweight Growth Curves

In this study, we have established gestational age-specific birthweight growth curves and percentile charts, segregated by both gender and ethnicity, and of immediate relevance to the local Singapore population. Birthweight growth curves are significant in the assessment of fetal health as well as postnatal growth, both which are key indicators of an infant's neonatal and future adult health. As previously highlighted, inadequate fetal growth places an infant at higher risk for mortality, metabolic diseases, complication and delayed neurological development (*Kramer et al., 1990*). Slow postnatal growth can lead to neurological delays while fast postnatal growth has been linked to the development of metabolic syndrome later in life (*Barker et al., 1989)*. Since birthweight growth curves are one of the commonly used tools in both clinical and epidemiological studies to assess fetal and postnatal growth, it is timely that birthweight growth curves relevant to the present local population and lifestyle are generated for accurate growth monitoring.

When comparison of the updated birthweight growth curves to the curves constructed by Cheng et al in 1972, significant differences are seen (*Cheng et al., 1972*). One limitation was that actual statistical test could not be done on the data comparison. However, aggregate mean comparison still shows significant differences in the 30-40 year gap between the two data sets. This proves many medical advances have been made that has improved antenatal care, maternal access to nutrition and preterm birth viability.

With these updated birthweight growth curves, we hope to improve the identification of small for gestational age (SGA) infants, defined as infants weighing less than the 10th percentile of the birth cohort. Although SGA infants may be physiologically healthy, such a classification facilitates the identification of neonates that may have faced *in utero* growth-restriction. It is well known that infants with intrauterine growth restriction (IUGR) are at elevated risk of postnatal complications and metabolic dysregulation (*Chatelain et al., 2000*). Other studies between Chinese and Caucasian populations also demonstrate the contribution of ethnicity to differing mean birtweights and fetal growth ratios (*Arbuckle et al., 1993*) *(Roberts and Lancaster., 1999*) (*McCowan et al., 2004*) (*Festini et al., 2004*) (*Hsieh et al., 2006*) (*Rios et al., 2008*). Yet in Singapore, many hospitals solely use World Health Organisation (WHO) guidelines for low birthweight infants as a proxy for identification of high-risk IUGR infants (*WHO/UNICEF., 2004*). This classification by birthweight alone provides limited valuable information on the infants and a correction for gestational age should be included. This underlines the importance of developing locally relevant gestational age-specific birthweight growth curves and percentile charts.

Typical gestational age-specific birthweight growth curves and percentile charts include data points from 37 - 41 weeks. With increasing maternal age and primiparity, premature births are less uncommon. Though premature infants are more likely than fullterm infants to have experienced IUGR, the current literature does not provide sufficient distinction between premature and fullterm infants in their early postnatal growth trajectory, as measured by weight. Hence, statistically meaningful gestational age-specific birthweight data from 34 - 37 weeks have been included in our study to act as a useful indicator of the health and morbidity of premature neonates.

One possible limitation of this study is the accuracy of documented gestational age. In the absence of early ultrasound estimations, gestational age is typically estimated from the reported last menstrual period. Since this can be confounded by bleeding in early pregnancy, a common symptom, recall bias is easily introduced to these dates. In this study, gestational age was determined by obstetricians using a combination of ultrasound and maternal self-reports a routine clinic procedure in the first or second trimester.

Other possible limitations were measurement errors through operator or equipment inaccuracy were minimal. Birthweight measurements were made in a clinical setting with nurses trained in correct usage of the digital scales. Scales were calibrated regularly throughout the duration of data collection, minimizing individual weighing errors. However, to reduce any inadvertent errors in the data set, extreme outliers were also removed.

A concern of significance is the use of a single centre in a study intended for population-wide application. The NUH is a university tertiary hospital responsible for a portion of Singapore's births a year. With the restructuring of public hospitals and the availability of comprehensive care at NUH, patients electing to deliver at our study centre of choice are fairly representative of the overall socio-economic profile in Singapore. Private hospitals in Singapore receive over 50% of all births, and while it would be advantageous to include these records, patient privacy restrictions prevent such access. As yet, national birth forms do not specify discrete birthweights, but record only birthweight ranges of individuals. Therefore, despite the inevitable discrepancies of a single centre study, the present data obtained from NUH is a reasonable representation of the local population with specific data fields available for creating local birthweight growth curves and percentile charts.

Future work can include records from other restructured public hospitals in Singapore to improve sample sizes. Additionally, data from the Singapore National Registry of Births and Deaths (SNRBD) that contains useful information including ethnic group, gender, gestational age, type of birth (singleton, twin, triplet etc.) and total number of live born children (including current pregnancy) can be easily accessed electronically. Unfortunately, individual birthweight ranges, and not discrete weights are captured, and we surmise that simple improvements to national record collection would enhance the usability of this data for future birthweight growth curves.

In addition to birthweight, morphometric measurements at birth such as body length and head circumference are easily obtained. Combined as a body proportionality index, these measures have also shown to correlate to infant growth (*Olsen et al., 2009*). As such, we anticipate that encouraging local hospitals to routinely include such statistics in birth records that will aid in future evaluations of similar data.

With the overall increase in mean birthweight over the past three decades, and rising global incidence of obesity, it is important to carefully analyze this trend. Alongside inherent maternal factors that may contribute to this increase in birthweight, changes in the processing and nutritional composition of today's foods may introduce new angles for examining the cause and effect leading to an emerging metabolic catastrophe among populations.

5.2 Influence of Gender and Ethnicity on Birthweight Growth Curves

In this study, we present an update to local birthweight growth curves and percentile charts that were previously developed without accurate gender or ethnic distinctions, both factors that we have shown to affect infant growth trajectories. The statistically significant differences in birthweight between male and female infants we observed are consistent with many studies in other populations (*Millis et al., 1954*) (*Kramer et al., 1990*). Although these differences appear subtle (2.25% - 4.28% between genders, across gestational ages), the functional implications of these changes are unknown, yet are linked to gender-specific biological pathways that require further examination.

Statistically significant differences in birthweight were also observed among the three major ethnic groups in Singapore (2.72% smaller - 3.12% larger), across gestational ages. While previous studies have demonstrated significant differences in the mean birthweights among the three races (*Cheng et al., 1972*) (*Hughes et al., 1986*) (*Viegas et al., 1989*), our study appears to be the first in the local population to further stratify this by gender, providing a more accurate view of the contribution of specific ethnicity to birthweight. An overview in Figure 20 and Table 29 demonstrates the change in mean birthweight for each ethnic group across the past three decades in Singapore. Through this, we observed the mean birthweight of Chinese infants begin declining from 1982 – 1983 onward, but have bottomed out from 1994 to the most recent data from 2000 - 2008. While Indian infant birthweights also began to decline from 1982 onward, the average birthweight continues to decline yearly. In Malay infants, a birthweight decline only begins twelve years later, from 1994 onward. These observed trends may be associated with genetic, dietary and environmental factors, and support the need to establish reference birthweight growth curves specific to individual ethnic groups.

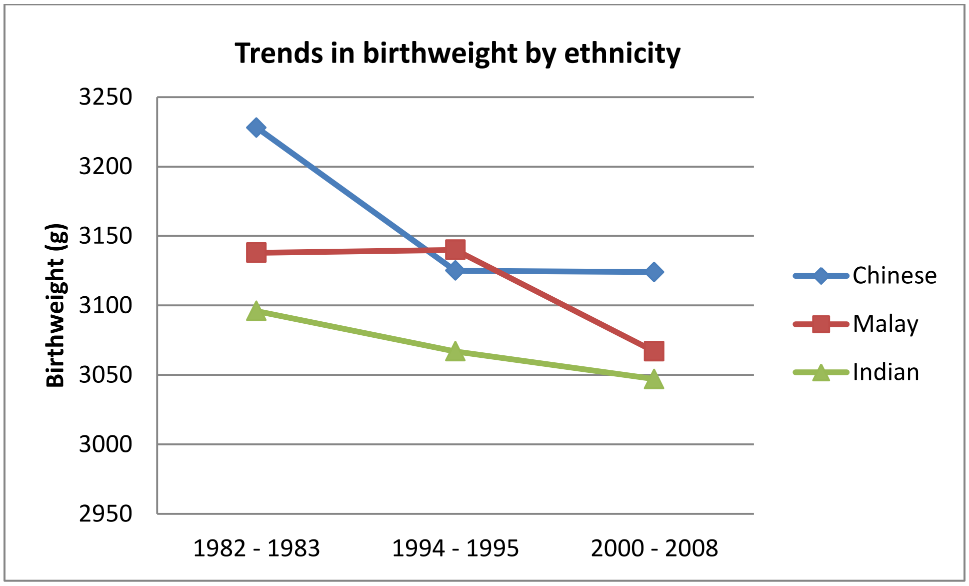


Figure 21: Trends in birthweight by ethnicity from 1980's to present.

		Mean Birthweight (g)		
Author	**Year**	**Chinese**	**Malay**	**Indian**
Viegas et al	1982 - 1983	3228	3138	3096
Tan et al	1994 - 1995	3125	3140	3067
	2000 - 2008	3124	3067	3047

Table 29: Mean birthweight by ethnicity from 1980's to present.

One limitation of this data set is the accuracy of infant ethnicity, since ethnicity was categorized by maternal ethnicity alone. Paternal ethnic background was not available through hospital records, hence infants with mixed ethnic backgrounds were not differentiated in the analysis. It is clearly evidenced by the low proportion of Chinese (44.4%), with higher proportion of Malays and Indian infants reflected in our study. Thus it was not reflective of the true ethnic distribution of the local paediatric population

(~70% Chinese) and therefore limits the representativeness of the cohort and the ethnic-specific birthweight growth curves generated.

One area of potential research could be the study of neonatal mortality and morbidity within the sample population, stratified by ethnicity and gender. Many previous studies have investigated the correlation between neonatal mortality and morbidity with birthweight, an indicator of infant health risk. With sufficiently large data sets culled from national databases, the increased sample sizes should facilitate a more comprehensive study of public health risk in specific ethnic populations.

5.3 Maternal Factors That Affect Birthweight

As previously discussed in the literature review, it is known that many maternal factors closely associate with birthweight, since fetal growth results from both genetic and environmental contributions. Of this, a major non-genetic contribution arises from maternal factors, and we perceived that closer examination of these factors would provide insight into our data. For example, as primiparous women typically give birth to infants of a lower mean birthweight, the increasing trend for smaller families and elevated initial maternal age may impact the resultant average population birthweight. Our data set is reflective of this trend, with 17.46% of primiparous mothers aged 35 years or greater (*Han-peter and Billari Jos'e., 2002*) (*Suzuki et al., 2006*). More adverse drops in birthweight were evident in mothers of advanced age (>41 years old). Older primiparous mothers are known to be at elevated risk of preterm births and SGA infants (*Lisonkova et al., 2010*), as well as other obstetric conditions such as placenta previa, placental abruption and increased risk for perinatal loss with odd ratios (adjOR) of 2.2 (*Cleary-goldman et al., 2005*). These results highlight the importance of pre and postnatal counselling and care for this group at risk for adverse outcomes.

As seen with other populations and also in our data, primiparity is also compounded by age in adolescent pregnancies (maternal age < 20 years old), resulting in IUGR conditions for infants. This is attributed in part to the differential nutrient compartmentalization and the anabolic drive to retain nutrients for maternal somatic growth (*Gluckman et al., 2004*). Slower *in utero* growth may be associated with increased allocation of nutrients to adipose tissue during development, leading to accelerated weight gain during childhood and a concomitant increase in risk of adult coronary heart disease, hypertension and type 2 diabetes mellitus (*Gluckman et al., 2008*).

Medical conditions such as gestational diabetes or hypertension can arise in women. Among infants born to women with gestational diabetes, we observed a 78.7 g increase in birthweight (*P <0.05*), as compared with healthy women. Infants born to mothers with gestational diabetes are more likely to be macrosomic, and face possible delivery complications as well as an increased risk of developing metabolic syndrome. The increased prevalence and earlier onset of obesity have implications for perpetuating the cycle of obesity and insulin resistance in subsequent generations (*Boney et al., 2005*). Therefore, as part of early intervention programs, expectant mothers should be advised on lifestyle maintenance for the wellness of their children. In our current practice, only women with risk factors are advised to do OGTT and thus this might missed out on analysis of women with undiagnosed diabetes mellitus.

Hypertensive disorders in pregnancy are a leading cause of maternal and perinatal mortality (*Steer et al., 2004*). Compared to healthy women, our data demonstrates a significant reduction in birthweight in infants born to women with gestational hypertension (49.4 g, *P <0.05*). Infants born to gestational hypertensive mothers are at heightened risk of preterm birth, SGA, prolonged maternal hospitalization and intensive infant neonatal care (*Vreeburg et al., 2004*). Early preventive and obstetric care has positively impacted this, improving the management of blood pressure in hypertensive mothers, thereby reducing the present incidence of LBW infants.

The majority of ART pregnancies is uncomplicated and result in normal healthy births. However, it is also clear that a higher proportion of ART pregnancies are associated with obstetrical and perinatal complications, and that children conceived through ART are at higher risk of abnormalities than spontaneously conceived children (*Allen et al., 2006*). Our data also suggests that singleton babies conceived via ART have a lower birthweight of 46.2g, compared with natural conception, and are at higher risk for adverse outcomes, including perinatal mortality, preterm delivery, and low birth weight, requiring close surveillance during pregnancy (*Green., 2004*). Current clinical practices surrounding ART are constantly evaluated to introduce improvements to both patient care and outcomes.

Despite the limited accessible information in our data set, future analyses will seek to provide a more comprehensive look at additional factors that might affect infant growth, such as social-economic status, maternal body mass index (BMI), pregnancy weight gain and maternal exposure to smoking and alcohol.

Additionally, the impact of paternal factors to infant growth is less well understood, but has also been reported to a smaller extent. While paternal age, height, and birthweight are associated with LBW, paternal occupational exposure and low education levels may be also associated with LBW (*Shah., 2010*). Paternal birth weight and body mass index (BMI) are also known predictors for placental and birth weight of the offspring (*L'Abée et al., 2011*).

Furthermore, the varied nutritional access and choices of today's communities may be an interesting extension of this present study. Poor maternal nutrition is one of the key "adverse environmental influences *in utero*," leading to compromised fetal and placental growth and adverse long term consequences (*Barker et al., 1992*). There is growing evidence that maternal nutritional status can alter the epigenetic state (stable alterations of gene expression through DNA methylation and histone modifications) of the fetal genome. This may provide a molecular mechanism for the impact of maternal nutrition on both fetal programming and genomic imprinting. Understanding the multiple roles of nutrients in DNA methylation (which can influence genome stability, viability, expression, and imprinting) will have a broad impact on reproductive health and disease prevention. Promoting optimal nutrition will not only ensure optimal fetal development, but will also reduce the risk of chronic diseases in adults (*Wu et al., 2004*). Understanding the mechanisms regulating fetal growth and development will be beneficial for designing novel therapeutic strategies to prevent and treat IUGR.

CHAPTER 6 SUMMARY AND CONCLUSION

6.1 Summary of Main Findings

In this study, we have established local relevant gestational age-specific birth weight growth curves and percentile charts specific to both gender and ethnicity. In comparison of present data to 1972 data from Cheng et al, it is evident that significant changes in birthweight have occurred over the 30 years gap. Indeed, advances in medical care have not only improved chances for survival of infants but also increase rate of healthier infants with the help of early prenatal care.

The analysis of gender differences was aimed at gathering information on whether gender-specific birthweight growth curves were fundamental. The statistically significant differences in birthweight between male and female infants confirmed that further stratification of the birthweight growth curves were essential. The ethnic group analysis observed here also portrays statistically significant differences in birthweight among the three ethnic groups in Singapore. This demonstrated differences support the need to establish reference birthweight growth curves specific to individual ethnic groups. Thus, our study seems to be the first in the local population providing a more accurate view by stratifying the birthweight growth curves by gender and ethnicity.

Over the 8-year period of data collection, we observed a gradual decrease in birth weight and an increase in the proportion of primiparous women giving birth in NUH. This mimics Japanese trends in towards rapidly falling birthweights in past few decades, and has been associated with a growing epidemic of childhood obesity (*Gluckman et al., 2007*). Our study demonstrate that smaller infants are typically born to adolescent mothers, primigravidas, ART pregnancies, as well as mothers with gestational hypertension gave birth to smaller babies. This is a major concern for these women, since their infants may be associated with an increased risk of subsequent development of cardiovascular disease (*Barker et al., 1989*), type 2 diabetes (*Hales et al., 1991*) (*Lithell et al., 1996*) (*Martyn et al., 1998*) and adiposity (*Kensara et al., 2005*) (*Gluckman et al., 2008)* due to that lower birth weight.

6.2 Conclusion

We have created updated local singleton birthweight growth curves and percentile charts by gestational age for the three main ethnic groups in Singapore. These are pertinent for use by local health care professionals in the accurate and early identification of growth-compromised neonates in order to provide appropriate intervention and care. Yet while birthweight is one correlate of growth, future developments should include molecular profiling at birth, for the identification of markers reflective of antenatal developmental and predictive of future phenotypic development. Importantly, it may provide an alternative to the current classification of infants using birthweights alone. Another important determinant for later obesity and disease risk lies in monitoring of the early postnatal growth pattern, and requires the use of longitudinal postnatal growth charts (*Ong et al., 2004*). Used together with birthweight growth charts, these provide a more holistic view of growth. With these tools, the early detection of accelerated growth pattern can also shed light on the development of insulin resistance and increased central adiposity.

Our data identifies some key factors that significantly affect birth weight, gender and ethnicity. Inherited and early-life events impact the acquisition of epigenetic marks that are themselves associated with increased chronic disease susceptibility (*Gluckman et al., 2009*), and we perceive that this will be an important overall direction of the field.

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APPENDIX A

Definitions

Appropriate for gestational age: 10^{th} to the 90^{th} percentile

Fullterm: birth between 37 to 42 weeks

Large for gestational age: greater than the 90^{th} percentile

Low birth weight: less than 2500 g

Preterm: birth prior to 37 weeks

Small for gestational age: less than the 10^{th} percentile

APPENDIX B

Abbreviations

AGA: Appropriate for gestational age

AdjOR: Adjusted Odds Ratio

ANOVA: Analysis of Variance

BMI: Body Mass Index

g: grams

GA: gestational age

IUGR: Intrauterine growth restriction

LBW: Low birth weight

LGA: Large for gestational age

OR: Odds ratio

SD: Standard deviation

SGA: small for gestational age

SNRBD: Singapore National Registry of Births and Deaths

WHO: World Health Organisation

APPENDIX C

Site Characteristics	
I C NUMBER	Mother’s identity number
Maternal Characteristics	
AGE	Mother’s age
NO_OF_LIV	No of living children (Parity)
DATE_OF_ DELIVERY	Date of delivery
ANTENATAL_	Type of antenatal disease
INTRAPARTU	Type of intrapartum cases
MODE_OF_DE	Mode of delivery
TYPE_OF_LA	Type of labour
SECONDARY_	Secondary complications
ETHNIC_GRO	Ethnic group
EDUCATION	Education level
OBSTETRIC_C	Obstetric complications
DURATION_O	Duration of labour
IND_CS	
PREVIOUS_C	Number of previous cesarean
ART_PREGNA	ART pregnancy
MATERNAL_D	Maternal death
Baby’s Characteristic	
GESTATION_	Gestational age in weeks
BIRTH_WEIGHT	Birthweight in grams
SEX	Gender of infant
CONGENITAL	Presence of congenital disease (Yes/No)
DEATH	Death of infant (Yes/No)
APGAR_1_MI	Apgar score at 1 minute (0-10)
APGAR_5_MI	Apgar score at 5 minutes (0-10)
ADMISSION	Admission to NICU (Yes/No)

Table 30: Data set field